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Preclinical Studies of Stem Cell Therapy for Heart Disease

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Abstract

As part of the TACTICS (Transnational Alliance for Regenerative Therapies in Cardiovascular Syndromes) series to enhance regenerative medicine, here, we discuss the role of preclinical studies designed to advance stem cell therapies for cardiovascular disease. The quality of this research has improved over the past 10 to 15 years and overall indicates that cell therapy promotes cardiac repair. However, many issues remain, including inability to provide complete cardiac recovery. Recent studies question the need for intact cells suggesting that harnessing what the cells release is the solution. Our contribution describes important breakthroughs and current directions in a cell-based approach to alleviating cardiovascular disease.

approach to alleviating cardiovascular disease.

Introduction to Stem Cell Therapy: Landmark Preclinical Studies/Appropriate Animal Models

Cardiovascular disease is the leading cause of mortality worldwide. However, despite improvements in pharmacological and interventional treatments, 1 in 3 men and 1 in 4 women die within a year of their first myocardial infarction (MI).[1] The prevalence of heart failure (HF) and MI requires new therapeutic approaches, which must be first tested in animal models to establish safety and therapeutic efficacy, before use in humans. The recent scientific statement of the TACTICS (Transnational Alliance for Regenerative Therapies in Cardiovascular Syndromes) group provides an overview of the many challenges associated with preclinical and clinical studies of stem cell therapy for heart failure[2] and is providing a series of guidelines and recommendations for moving this field forward.[2,3] Unlike pharmacological treatments, which primarily manage the disease, stem cell administration promotes the restoration of lost functionality. However, negative outcome trials and the recent debate on the efficacy of the human clinical cell–based therapy in patients with acute MI (AMI)[4] mean that we must continue to find better approaches that will ensure success in human trials.

Although myocyte necrosis leads to remodeling post-MI, this effect is secondary to a cascade of cellular changes that seem to be the primary cause of ventricular dilation, hypertrophy, and scar formation.[5] In contrast to the age-old paradigm that cardiac myocytes are terminally differentiated, the current consensus is that ≈0.5% to 2% of cardiomyocytes undergo mitosis annually.[6] In infarcted human hearts, myocyte growth becomes enhanced at the border zone after an ischemic event with up to 3- to 4-fold more dividing myocytes 1 week post-infarction than in end-stage HF.[7] Understanding and enhancing cardiomyocyte proliferation post-MI are central themes of regenerative medicine.

In early murine studies, mobilization of myeloid clonogenic cells from spleen and bone marrow (BM) was observed during wound healing.[8] Later discoveries noted the effects of neovasculogenesis after endothelial progenitor cells (EPCs) mobilized secondary to hind limb ischemia. Rabbits mobilize EPCs specifically from the BM after hind limb ischemia, which was enhanced after GM-CSF (granulocyte-macrophage colony-stimulating factor) administration.[9] These findings paved the way for the use of progenitor cell to treat

disease. During these early studies, there was no notion of intrinsic self-renewing cardiac cells. In 2003, this paradigm changed; cardiac stem cells (CSCs) that are self-renewing, clonogenic, and multipotent were observed in adult rat hearts.[10] Thus, began the concept that, with some help, the heart could heal itself. The controversy concerned the nature of that help. For many, the answer was which type of stem cell should be used to treat heart disease. The safety, efficacy, and fate of each cell line needed further research in animal models to determine not only which model was best to simulate human cardiac response but which of these various cell types should be studied further.

Small Animal Studies

For preclinical development, an appropriate animal model that accurately reflects human pathological conditions is essential. Cell and molecular studies provide important mechanistic data, and toxicity studies evaluate candidate drugs,[11] but a working heart is needed to evaluate and optimize treatments.

New therapies for cardiovascular disease are usually first evaluated in small animal models (rodents), a model that provides relatively rapid and economical testing and adequate group sizes to ensure sufficient statistical power. Recent technological advances in PET-MRI (positron emission tomography/magnetic resonance) imaging and echocardiography have improved the assessment of cardiovascular outcomes in rodents.[12] Mouse models do have inherent advantages but also some limitations. They can respond very differently than humans to treatment,[13] their hearts beat at 400 to 600 bpm, and they have a variety of anatomic differences with human hearts (reviewed by Santos et al[12]). Transgenic and knockout mice are widely available, making them particularly useful for assessing genetic factors and inducers of cardiovascular diseases. However, genetic changes can alter cardiac morphology, which can limit the advantages of these models.[12] Discrepancies between human and mouse embryonic stem cells (ESCs), including the expression of genes regulating apoptosis, cytokine expression, and cell cycle regulation, can further limit the relevance of mouse models.[14]

Rat heart mass is roughly 10-fold greater than mice, and surgical expertise is less demanding. The rat coronary ligation model was first described in 1979,[15] and ligation of the left anterior descending (LAD) coronary artery is the most widely used model for MI. A rat model of MI was instrumental in the evaluation and development of angiotensin-converting enzyme inhibitors[16,17] as prelude to clinical trials that resulted in the approval of captopril as a therapeutic intervention for HF after MI.[18] However, positive rat preclinical studies do not necessarily translate to successful clinical trials. Endothelin receptor antagonists, such as bosentan, improved survival and hemodynamic characteristics in the rat after MI,[19] but failed to show a benefit in humans with HF.[19]

Large Animal Studies

Cardiac repair studies show larger effects in rodents, increased left ventricular ejection fraction (LVEF) up to 20%, and normalization of LV function, in contrast to large animal studies (mean LVEF improvement ≈5%–7%).[20] This moderate benefit corresponds better to the results of clinical trials, giving realistic insight into the expected benefit of human cell–based cardiac therapies. The presence or absence of collateral coronary circulation is an important factor for choosing an adequate animal model for a particular study. Large animals such as pigs, dogs, or sheep satisfy many of these criteria. Dogs have an extensive collateral coronary circulation, whereas pigs and sheep have no functionally relevant vascular adaptation system, similar to humans.[21] Thus, a dog model is suitable for studying vascular adaptation to myocardial ischemia, whereas pigs and sheep are generally regarded as appropriate to assess the direct myocardial effects of hypoxic injuries.

Initial studies in canine hearts in the late 1970s paved the way to understand myocardial ischemia and the development of HF.[22] In a dog MI/reperfusion model, the angiotensin receptor blocker valsartan produced decreased infarct size and increased EF and improved diastolic function.[23] Ischemic cardiomyopathies can be simulated in canines through microembolization,[24] resulting in reduction of LVEF to <35%, a model that has been used for evaluation of several drugs for treating HF.[25] The drawback of these studies is that canines have a significantly more complex coronary circulation than humans, such that their maximal oxygen consumption is greater and their degree of reproducible infarct size more variable.[26] Therefore, despite the advantages of the canine, a better model was still needed. One such model is the sheep, where coronary anatomy is consistent with humans; there is a lack of significant collateral circulation, allowing for reproducible infarcts. However, sheep carry zoonotic disease, a problem not associated with other large animals, and ovine thoracic and gastrointestinal anatomy complicate detailed imaging, so is not ideal for typical transthoracic imaging studies.[27]

Swine cardiac anatomy compares favorably to that of humans. In the vast majority of cases, the large LAD and the dominant right coronary artery, supply the posterior interventricular septum and the atrioventricular node; and the minimal collateral flow, is also similar to humans.[28] Furthermore, adult Göttingen and Yucatan minipigs possess cardiac structure and function comparable to humans, including high mortality associated with large infarcts.[29] For chronic studies, they remain within a manageable weight range when compared with Yorkshire pigs.[29] By ligation of the LAD, MI can be induced by either open- or closed-chest methods. Open-chest surgery provides easy access to coronary arteries, visual control of contractility, and facilitates the generation of defined infarction

sites and sizes. However, closed-chest procedures avoid the thoracotomy-associated trauma of open-chest surgery[30] as in humans. Large animal studies are very expensive (10–100× higher than similar small animal studies), limiting the number of animals in a study. A major advantage of large animal studies is the ability to use imaging modalities identical to those for humans, resulting in similar measures and outcome parameters, increasing human relevance but also costs.

This overview of preclinical models for regenerative medicine demonstrates that each has inherent advantages and disadvantages. Small animal studies provide an initial indication of the potential of the intervention and must be further evaluated in large animals whose cardiovascular physiology more closely resembles humans. Only when a treatment provides sufficient therapeutic efficacy in large animals should it be moved to clinical trials.

Mesenchymal Stem Cells

Mesenchymal stem cells (MSCs; also called mesenchymal stromal cells) have been the most commonly used stem cell for treating cardiac dysfunction. MSCs are relatively easy to isolate and can be expanded significantly ex vivo. Their immunosuppressive properties and their lack of immunogenicity make them excellent candidates for cell therapy. However, the various methods of cell expansion, isolation and characterization, necessitated a consistent definition of MSCs (Figure 1). The Mesenchymal and Tissue Stem Cell Committee of the International Society for Cellular Therapy proposed distinct criteria: plastic adherence under standard culture conditions, positive for CD105, CD73, and CD90, and negative for CD45, CD34, CD14 or CD11b, CD79α or CD19, and HLA-DR (human leukocyte antigen- antigen D related) and the ability to differentiate into osteoblasts, adipocytes, and chondroblasts in vitro.[32] MSCs have an additional therapeutic advantage; they lack MHC class II antigens and not only fail to elicit an immune response (at least initially) but also downregulate host natural killer cells and T lymphocytes.[33] Similarly, xenotransplantation of human BM-derived MSCs (BM-MSCs) into murine[34] and later porcine[35] hearts revealed the ability of (a low percentage of) MSCs to integrate into the myocardium and differentiate into cardiomyocytes.

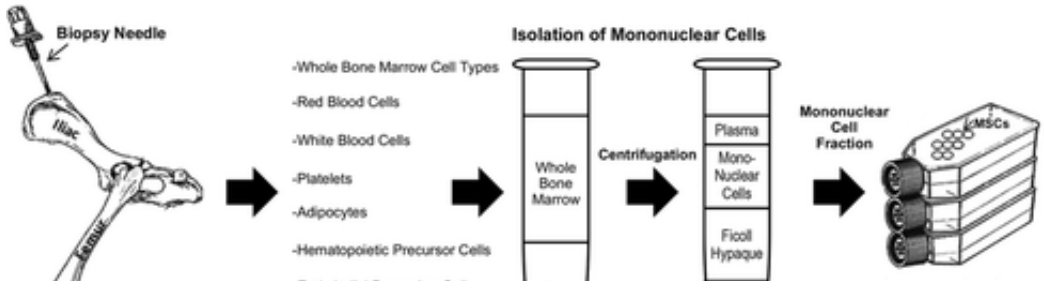

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Figure 1. Procurement and isolation of mesenchymal stem cells (MSCs). MSCs isolated from bone marrow and the mononuclear cells isolated by Ficoll density centrifugation. MSCs can be separated from other mononuclear cells by their plastic adherence in culture. Reprinted from Williams and Hare[31] with permission. Copyright ©2011, the American Heart Association.

Cells with similar characteristics to BM-MSCs are found in virtually every tissue[36]; however, most cardiac studies have used MSCs from BM or a few other tissues (although this trend may be changing) including adipose-derived and umbilical cord (UC) blood/Wharton's jelly–derived MSCs. BM- and adipose-derived MSCs most consistently differentiate into bone, fat, and cartilage and have the highest capacity for self-renewal.[37] Although circulating MSCs, which are thought to arise from BM, have long been debated as a source for future clinical use, they have produced contradictory results, reducing confidence in them as a source.[38]

BM-Derived MSCs

BM is of particular interest for stem cell therapy because it is a source of a variety of multipotent precursors (MSCs, mononuclear cells, and EPCs; see below). However, stem cells comprise only 1% to 3% of BM, the majority being lymphocytes; but there are other undesirable cells for cardiac repair: monocytes, pre-adipocytes, and osteoblasts.[39] An important property of MSCs is their ability to home to sites of injury, a property first demonstrated in a baboon lethal radiation model.[40] Murine studies demonstrated that MSCs migrate to ischemic cardiac tissue after intravenous infusion.[31] Factors thought to play a role in these migratory and stimulatory properties include the stem cell factor/c-kit (CD 117) ligand–receptor complex.[41,42] Once the ability of MSCs to home was recognized, studies focused on improving cardiac function, which were encouraged by the ability of murine BM-MSCs to become functional cardiomyocytes when treated with 5-azacytidine (5-aza), a demethylase and cytosine analog. MSCs begin beating after 2 weeks of 5-aza exposure, and after 3 weeks, the beating becomes synchronized.[43]

Overall, most, but not all, studies in small and large animals, for both AMI and chronic MI, show improved cardiac structure and function after BM-MSCs administration (see Narita

and Suzuki for review[44]). Determining the precise mechanism(s) is difficult because few cells remain in the myocardium over time. The consensus is that beneficial MSC effects are primarily paracrine, involving not only secretion of growth factors (Table) but also microvesicles and exosomes.[46,47] The efficacy of these cells also seems to be influenced by the route of injection.[48]

Table. Paracrine Factors Secreted by MSCs

Secreted Factor	Function
Proangiogenesis	
FGF-2	Induces endothelial and smooth muscle proliferation
FGF-7	Induces endothelial cell proliferation
MCP-1	Induces angiogenesis; recruits monocytes
PDGF	Smooth muscle proliferation
PlGF	Promotes angiogenesis
TGF-β	Vessel maturation
VEGF	Endothelial cell proliferation, migration, tube formation
Remodeling of extracellular matrix	
MMP1	Loosens matrix; tubule formation
MMP2	Loosens matrix; tubule formation
MMP9	Loosens matrix
PA	Degrades matrix
TNF	Paracrine; stem cell proliferation

TNF-α	Degrades matrix; modulates cell proliferation
Stem cell proliferation, recruitment, and survival	
bFGF	Enhances proliferation of endothelial and smooth muscle cells
G-CSF	Increases proliferation and differentiation of neutrophils
IGF-1	Regulates cell growth and proliferation; inhibits apoptosis
M-CSF	Increases proliferation and differentiation of monocytes
Tβ4	Promotes cell migration
SDF	Progenitor cell homing
SFRP1	Enhances cell development
SFRP2	Inhibits apoptosis; enhances cell development
Immunomodulatory	
HO1	Inhibits T-cell proliferation
HGF	Inhibits $CD4^+$ T-cell proliferation
IDO	Inhibits innate and adaptive immune cell proliferation
iNOS	Inhibits inflammation
IL-6	Regulates inflammation; VEGF induction
PGE_2	Inhibits inflammation

bFGF indicates basic fibroblast growth factor; FGF, fibroblast growth factor-7; G-CSF, granulocyte colony–stimulating factor; HGF, hepatocyte growth factor; HO1, heme oxygenase-1; IDO, indoleamine 2,3-dioxygenase; IGF, insulin-like growth factor; IL

oxygenase-1; IDO, indoleamine 2,3-dioxygenase; IGF, insulin-like growth factor; IL, interleukin; iNOS, inducible nitric oxide synthase; MCP, monocyte chemoattractant protein-1; M-CSF, macrophage colony–stimulating factor; MMP, metalloproteinase; MSCs, mesenchymal stem cells; PA, plasminogen activator; PDGF, platelet-derived growth factor; PGE_2, prostaglandin E_2; PlGF, placental growth factor; SDF, stem cell–derived factor; SFRP, secreted frizzled-related protein; TGF, transforming growth factor; TNF, tumor necrosis factor; Tβ4, thymosin-β4; and VEGF, vascular endothelial growth factor. Reprinted from Williams and Hare[31] with permission. Copyright ©2011, the American Heart Association.

Small Animal Studies

Orlic et al[49] were among the first to show an improvement in cardiac function after intramyocardial injection of (eGFP [enhanced green fluorescent protein] labeled) lineage $(Lin)^-/c\text{-}kit^+$ BM-derived stem cells into female mice in an AMI model. They observed $eGFP^+$ cardiomyocytes, endothelial cells, smooth muscle cells, and vascular structures in the infarcted region of the heart, leading to the conclusion that BM-derived cells can engraft and repair myocardium in vivo.[49] Since then small animal studies have reproducibly shown favorable outcomes after AMI. Reduction in infarct size and fibrosis, with enhancement of LVEF and vasculogenesis, is among the common findings in the animal trials.[44] Additional benefits include decreased apoptosis, decreased fibrosis, increased VEGF (vascular endothelial growth factor) expression, and increased regional blood flow in the infarct zone.[48,50]

An emerging use for stem cells, particularly BM-MSCs, is in the treatment of idiopathic dilated cardiomyopathy (DCM). Given the lack of distinct areas of hypoperfusion and systolic dysfunction in the absence of coronary disease, it is a challenge to reverse this effect.[51] One group established a DCM model in rabbits. BM-MSCs were pre-incubated with 5-aza to induce differentiation into cardiomyocyte-like cells and injected directly into the myocardium resulting in an increase in LV end-systolic pressure and a decrease in LV end-diastolic pressure. There was also an attenuation of myocardial fibrosis with an increase in VEGF.[52] Similarly, in a rat DCM model, there was a noticeable decrease in LV end-diastolic pressure and an increase in LV end-systolic pressure.[53]

Intramyocardial injection of BM-MSCs after AMI produced a significant reduction in fibrosis and a noticeable engraftment of MSCs which differentiated into cardiomyocytes. Infarct size and the number of vascular cells in the myocardial structure were markedly improved.[54] Although this study showed high engraftment of MSCs, most studies do not, with engraftment rates ranging from 6% to 12% of injected cells.[55] In an effort to improve engraftment, Simpson et al[56] developed an epicardial patch composed of human BM-

engraftment, Simpson et al[56] developed an epicardial patch composed of human BM-MSCs and secured it to the acutely infarcted region. One week later, 23% of the cells engrafted into the myocardium. At 4 weeks, there was less LV dilation and better preservation of wall thickness, but without improvement in ventricular function when compared with controls. The authors attribute the latter finding to the small number of MSCs (1×10^6) that were initially embedded in the patch.[56]

Large Animal Studies

Both autologous and allogeneic BM-MSCs produce beneficial effects in swine AMI[30,35,57,58] and chronic[29,59–62] MI models. Early studies highlighted the engraftment and trilineage differentiation (cardiomyocyte, endothelium, and vascular smooth muscle) of MSCs.[58,60] In a porcine model, labeled allogeneic BM-MSCs injected into the myocardium after AMI were found in the infarct region 8 weeks later. These cells expressed VEGF and specific cardiomyocyte proteins that suggested an upregulation of vasculogenesis and myocyte differentiation. Imaging and gross inspection showed an increase in LVEF and in subendocardial thickness and a decrease in scar size in the cell-treated group.[57,63] Although some engraftment occurs, at least in the short term, the consensus is that MSC therapy provides therapeutic efficacy through secretion of growth factors, microvesicles, and exosomes (see below). Of particular importance is the observation that intramyocardial injection of BM-MSCs post-MI in Yorkshire pigs increased proliferation of endogenous CSCs.[58]

In chronic ischemic cardiomyopathy settings, BM-MSC therapy has focused on the ability of MSCs to reduce fibrosis and reverse remodeling. Reduced myocardial thinning in the infarcted zone was reported in the treatment group after gross inspection. Histological analysis revealed MSC engraftment up to 6 months post-implantation.[64] Schuleri et al[61] assessed whether cell dose is an important parameter. They injected either 20×10^6 versus 200×10^6 autologous cells via an intramyocardial route 12 weeks post-MI. Delayed enhancement showed a decrease in infarct size in the low-dose group and a decrease in infarct volume in the high-dose group. Myocardial wall thickening was noted in both groups. Contractility was increased in the noninfarcted region in both MSC groups[61]; however, the contractility in the infarcted region was increased in only the high-dose group. Quevedo et al[60] similarly tested the efficacy and safety of allogeneic MSCs in a swine model of chronic MI. Animals were injected via a transendocardial route. Twelve weeks post-injection, the MSCs had engrafted, vasculogenesis flourished, and myocardial blood flow, LVEF, and regional contractility had improved when compared with placebo.[60]

Stro-1$^+$ BM-MSCs

A subset of BM-MSCs, BM progenitor cells (MPCs), has gained some interest over the

past several years. These Stro-1$^+$/CD34$^-$ cells are an immature subfraction of BM-MSCs.[65] In addition to their ability to self-renew, they can differentiate into chondrocytes, adipocytes, chondroblasts, and smooth muscle cells. Proponents of this subtype argue that MSCs in general are hard to define completely and this cell subtype can be isolated by immunoselection and has an enhanced ability to replicate and differentiate compared with traditional MSCs.[66] Animal studies with MPCs have produced promising results.

Large Animal Studies

Acutely infarcted sheep received intracoronary injection of allogeneic MPCs. There was a 40% decrease in scar size and a 50% increase in vascular density.[67] Another group used echocardiography to guide the injection of intramyocardial allogeneic MPCs into sheep 4 weeks post-MI. An increase in LVEF, wall thickness, and vascular density was reported.[68] In a nonischemic model, transendocardial administration of ovine allogenic cells produced decreased LVESV, stabilization of LVEF, and decreased fibrosis.[69]

Adipose-Derived Stem Cells

Adipose-derived stem cells (AdSCs) are generated from enzymatic degradation of adipose tissue, which yields the stromal vascular fraction. The stromal vascular fraction then undergoes adherent culture purification to CD105$^+$/CD34$^-$ AdSCs. Isolation of adipose tissue (liposuction) is relatively inexpensive and is much less invasive compared with BM aspiration and yields a large number of cells. AdSCs secrete a similar variety of growth factors as BM-MSC,[70] and ex vivo can be differentiated into cardiomyocytes, endothelial cells, vascular smooth muscle, and even pacemaker cells.[70] AdSCs, like BM-MSCs, are immunoprivileged because of lack of MHC class II, and they can improve the function and minimize the immune rejection of EPCs.[71] Given those similarities, their ease of isolation, and the success of BM-MSCs, there is considerable interest in the potential of AdSCs to improve the function of a failing heart.

Small Animal Studies

Although AdSCs and BM-MSCs overall behave similarly, an interesting study was performed by Rasmussen et al[72] who isolated AdSC and BM-MSCs from an elderly patient with ischemia. These cells were injected intramyocardially into rats 1 week post-MI. Neither cell type promoted angiogenesis or reduced infarct size, but the AdSCs improved LVEF.[72] This result suggests differences in effi

Although not currently being used in human trials, brown promise in animal studies. Studies in rats demonstrated subpopulations of brown adipose tissue reduce infarct s through the induction of cardiomyocyte proliferation.[73,7

are needed because most of the preclinical studies were tissue in mice or rats in an acute setting.

The therapeutic effects of adipose-derived cardiomyoge AdSCs that are CD90^{-} and retain the ability to express c proteins, were studied. Three days after ligation of the L adipose-derived cardiomyogenic cell into the coronary a exhibited a reduction in remodeling, increased vasculog

Large Animal Studies

A porcine model introduced AdSC via coronary artery in days later, analysis showed a noticeable decrease in the EF, vascular density, and wall thickness.[76] Most studies however, 1 group used rabbits to study chronic ischemia rabbits were injected with AdSCs directly into the infarct associated with a greater vascular density, LVEF, and im weeks post-injection compared with controls. However, AdSCs are very beneficial. Intracoronary administration perfusion but not LVEF after AMI in a porcine model,[77] b affected the efficacy of the cells (see below). Improved p were also seen on administration of AdSCs into humaniz only with the highest concentration of AdSCs (4×10^6 cel no effect on either parameter.[78]

Umbilical Cord MSCs

Fibroblast-like cells were isolated from the connective ti the early 1990s[79] and became a source of MSCs. These their noninvasive ease of extraction, high MSC yield, an limited preclinical data on UC blood and UC matrix MSC currently underway. Transcriptional signature compariso blood MSCs indicates distinct gene expression profiles. exhibit higher expression of genes associated with cell a immune system functioning neurotrophic support, sugge better than BM-MSCs for neurodegenerative diseases.[8

Small Animal Studies

One group tested a murine model in an acute ischemic s intramyocardial injection of human UC matrix MSCs, the weeks post-MI, but there were no differences in infarct size compared with controls, and

weeks post-MI, but there were no differences in infarct size compared with controls, and both groups experienced ventricular wall thinning and dilation. Histologically, there was a lack of cell engraftment into the myocardium, which may indicate that the mechanism of ventricular preservation was because of a paracrine effect.[82] A transgenic mouse model with DCM received intramyocardial injections of human UC MSCs. One month later, the LVEF was increased, the heart weight:body weight ratio decreased by 10%, and chamber dilation reduced in the cell-treated group compared with placebo control mice. Histologically, VEGF and IGF-1 (insulin-like growth factor-1) were upregulated and vasculogenesis increased, whereas apoptosis, fibrosis, and vacuolization all decreased.[83] Rat DCM was treated with human UC matrix MSCs, resulting in reduced fibrosis and cardiac dysfunction. The authors concluded that these cells worked, at least in part, by inhibiting TNF (tumor necrosis factor)-α and TGF (transforming growth factor)-β1/Erk1/2 (extracellular signal–regulated kinase 1/2) signaling.[84] Roura et al[85] created a fibrin patch to promote the efficacy of UC blood MSC in acutely infarcted mice. The cells were retained within the patch for 4 weeks post-implantation. The patch-treated group yielded a smaller infarct scar (16% versus 49%) and increased subjacent myocardial angiogenesis compared with controls.[85] Latifpour et al[86] injected human UC matrix MSCs into the cyanotic region in a rabbit model of AMI. Thirty days later, LVEF was significantly improved with evidence of cell engraftment, decreased scar size, and chronic inflammatory markers.[86]

Large Animal Studies

Zhang et al[87] were the first to use human Wharton's jelly MSCs in swine after AMI. Six weeks after intramyocardial injection of cells, they observed improved perfusion in the cell-treated group, engraftment of injected cells, some of which seemed to have differentiated into cardiomyocytes and vascular endothelial cells. Furthermore, there was an increased proliferation of immature cardiomyocytes expressing c-kit$^+$, reduced apoptosis, and increased LVEF in the treated group compared with placebo.[87]

Overall, MSCs obtained from a variety of tissues have demonstrated therapeutic efficacy. They tend to work similarly, reducing scar size and immune response, increasing perfusion, and improving cardiac function. Although MSCs have been studied for a majority of stem cell studies, many other stem cells have promoted cardiac repair.

CSCs/Cardiac Progenitor Cells

A microenvironment or niche exists within the heart that is thought to play a critical role in maintaining stem cells in an undifferentiated state, but releasing them from this hold when necessary. Within the niche, stem cells give rise to cardiac progenitor cells, which migrate to sites of myocardial injury in an effort to repair the damage. Unfortunately, these

endogenous stem cells quickly become depleted after large infarctions,[88] resulting in incomplete healing and subsequent HF. Although the idea of self-renewing cells in the heart was once considered unlikely, this concept is now well accepted and includes myocytes[89–91] and stem cells within the myocardium.

Small Animal Studies

The landmark study where c-kit$^+$ CSCs were initially identified was conducted in mice. These cells were Lin$^-$/c-kit$^+$ (CD117; the receptor for stem cell factor), previously found in neonatal myocardium,[92] were isolated from the heart, and clonally expanded in culture.[10] These Lin$^-$/c-kit$^+$ cells were injected into the peri-infarct region after MI in rats. The resultant immunohistochemical staining and histological examination showed that c-kit$^+$ cells self-renew and act in a clonogenic and multipotent manner to produce cardiomyocytes, smooth muscle cells, and endothelial cells.[10] Oskouei et al[93] directly compared human c-kit$^+$ CSCs with human MSCs for cardiac repair in an AMI model in immunodeficient mice. The CSCs exhibited more engraftment and differentiation, produced greater improvements in remodeling and hemodynamic parameters and were equally able to reduce scar size compared with 30-fold more human MSCs.[93] Overexpressing Pim1 kinase in c-kit$^+$ human CSCs augmented their retention within the myocardium and their therapeutic efficacy in both a mouse[45] and swine[94] model of AMI.

Other notable CSCs include cells expressing stem cell antigen-1 (not found in humans), side population cells (low in c-kit$^+$), and islet-1 transcription factor cells (only found during the neonatal period), none of which to date have been used in clinical trials.[95] Epicardium-derived stem cells, while similarly not yet tested in clinical trials, may be a candidate cell type, but require more preclinical testing. During murine cardiac development, these Wt1$^+$ cells develop into functional cardiomyocytes.[96] They are multipotent, resemble MSCs, participate in cardiac development, and likely have the potential to promote myocardial repair.[97] Determining the importance of c-kit$^+$ CSCs for cardiac development and as a cell therapy for heart disease has been fraught with controversy. Although some investigators minimize the role of CSCs,[98] recent studies have clarified their origin and differentiation capabilities.[99]

Large Animal Studies

In a chronic ischemic swine model, intracoronary administration of c-kit$^+$ CSCs into pigs 3 months post-MI demonstrated the therapeutic efficacy of these cells. Beginning 1 month post-injection, the LVEF rose in the cell-treated group and there was a regional increase in cardiac function. CSCs engrafted and some differentiated into cardiomyocytes and vascular structures.[100]

Cardiospheres and Cardiosphere-Derived Cells

Cardiospheres are a heterogeneous group of stem cells isolated from myocardial biopsies, that form clusters. The cells, initially isolated from human myocardial biopsies, express stem cell–related antigens, and some cells spontaneously undergo cardiac differentiation. On expansion ex vivo, these cells are called cardiosphere-derived cells (CDCs).[101] CDCs have been studied as an autologous and allogeneic therapy for MI. Recently, it was determined that the $CD105^{+}/CD90^{-}/c\text{-}kit^{-}$ population of CDCs represents the therapeutically active cell fraction.[102]

Small Animal Studies

Coronary infusion of allogeneic CDCs into rats post-MI reduced scar size and increased cardiac function, myocyte cycling, and angiogenesis.[103,104] Allogeneic CDCs have also proved effective in revitalizing senescent rats.[105]

Large Animal Studies

CDC treatment of AMI[106] and chronic[107] MI in the pig produces beneficial results. Recently, Gallet et al[108] demonstrated that CDC therapeutic effects are likely mediated via CDC-derived exosomes.

BM Mononuclear Cells

BM mononuclear cells (BM-MNCs) are a heterogeneous cell population which includes MSCs, hematopoietic cells, EPCs, and others. BM-MNCs are easier to isolate than the component population and have been tested in numerous studies,[109] but in clinical trials seem to be less effective than MSCs.[110]

Small Animal Studies

Early studies of MI in rats showed that intramyocardial injection BM-MNCs promoted significant vasculogenesis without an associated increase in VEGF or FGF (fibroblast growth factor) at 2 weeks post-injection. However, there was a subsequent decrease of vascularity in the 4-week group, which may have been secondary to the maturation of the scar.[111] A cryoablation rat model tested mixing BM-MNCs into a fibrin matrix. Eight weeks later, there was a greater enhancement of neovascularization in the cell+matrix group compared with cells alone.[112]

Large Animal Studies

Promising results were seen after direct BM-MNCs injection into the peri-infarct zone after LAD ligation. LVEF increased, the perfusion defect markedly decreased, and the LV end-

diastolic volume:body weight ratio decreased in the treated group.[113] Alestalo et al[114] showed a direct correlation between improvement in LVEF after AMI and the number of retained cells seen on postmortem histological examination. Therefore, direct contact and retention of BMCs in ischemic tissue may be critical. Fuchs et al[115] were the first to establish the safety of transendocardial cell injection in a swine chronic ischemia model. They reported improved perfusion of the ischemic zone and enhancement of wall thickening 4 weeks post-MI,[115] as well as an increase in vascularization of the myocardium and a decrease in scar size in the treated group. However, cardiac function did not change in either group.[116] A canine model showed the most favorable effects with regard to ventricular function[117] and in sheep no difference in function reported in cell-treated animals compared with controls.[118] Nonetheless, in the preclinical setting, BM-MNCs have produced enhancements to neovascularization and reduced scar size; however, large animal models have shown variable effects in ventricular function.

Hematopoietic and EPCs

The transplantation of BM-derived cells into mice led to the discovery of a hematopoietic source of regenerative cells. Hematopoietic stem cells and EPCs both are $CD34^+/CD133^+$ cells and can transform into myeloid and lymphoid cells or once mobilized from the BM into the blood after tissue injury can subsequently become endothelial cells, which can promote neovascularization.[119]

Small Animal Studies

Murine AMI studies have demonstrated enhanced neovascularization, EF, decreased scar size, and differentiation of hematopoietic stem cells into endothelial cells in myocardial tissue.[120–122] Manipulating the EPCs provides improved repair potential. Thal et al[123] compared the ability of EPCs or epigenetically reprogrammed EPCs to differentiate into cardiomyocytes and promote cardiac repair post-AMI. The unmanipulated EPCs reduced infarct size, reduced LV volume, and increased capillary density, but the manipulated (5-aza, valproic acid) EPCs did all 3 significantly better. Furthermore, the manipulated EPCs engrafted and differentiated into cardiomyocytes.

Large Animal Studies

EPC-conditioned media are cardioprotective after AMI in a swine model. Neutralizing IGF activity in the media abrogated these effects.[124]

Pluripotent Stem Cells

Transducing mouse fibroblasts with a set of transcription factors (Oct4, Sox2, Klf4, c-MYC) now known as the Yamanaka factors produced novel pluripotent cells, induced

MHC) now known as the Yamanaka factors produced novel pluripotent cells, induced pluripotent stem cells (iPSCs). iPSCs have surface markers and functional properties similar to ESCs[125] and can be differentiated into hormone-responsive beating cardiac cells that mimic ESC-derived cardiomyocytes.[126] Produced from autologous tissue, immune rejection and ethical concerns are no longer an issue. Using iPSC-derived and ESC-derived cardiomyocytes reduces the tumor threat, but the cells remain immature and have limited ability to restore cardiac function.[127]

Small Animal Studies

Initial animal studies used direct injection of iPSCs into the myocardium of mice, resulting in engraftment, improved cardiac function, increased wall thickness and reduced fibrosis.[128] However, iPSC-derived cardiomyocytes engrafted long term in a rat model of MI but failed to produce beneficial effects.[129]

Large Animal Studies

The first studies in a large animal model examined coinjected human iPSCs and human MSCs in acutely infarcted swine. The human iPSCs enhanced vasculogenesis, but the combination of cells increased capillary density to a greater extent, likely secondary to the decreased rates of apoptosis.[130] Kawamura et al[131] placed a sheet of dermal fibroblast-derived human iPSC-derived cardiomyocytes over the infarcted area in an ischemic swine model, which produced improved cardiac performance, angiogenesis, and an attenuated LV remodeling 8 weeks post-implantation. Neither of these 2 studies reported tumor formation. Both ESC-derived cardiomyocytes and iPSC-derived cardiomyocytes have been studied in nonhuman primates. Macaques received 1×10^9 human ESC-derived cardiomyocytes 2 weeks post-MI via intramyocardial delivery.[132] After 3 months, the cells continued to mature (albeit incompletely). Importantly, the cells engrafted, promoted extensive remuscularization of the infarcted tissue, exhibited regular calcium transients and no evidence of tumors or of cells outside the heart. All of these monkeys exhibited arrhythmias.[132] Zhu et al[133] administered human PSC–derived cardiovascular progenitors into the myocardium of male cynomolgus monkeys 30 minutes post-MI. Cells were present 3 days later but not after 140 days, despite a modified immunosuppressive regimen. Apoptosis was reduced and cardiac function improved by the cells. However, no remuscularization was seen.[133]

Combination Stem Cell Therapy

To improve therapeutic efficacy, a new approach is to combine cells. Small and large animal studies have combined progenitor cells. Cells combined with angiogenic/growth factors increased vasculogenesis and cell survival, reduced apoptosis, and enhanced cardiac function.[33]

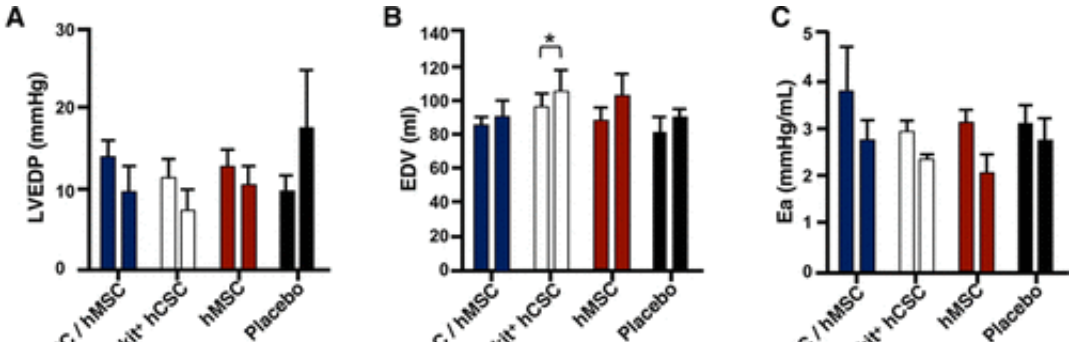
cardiac function.

Small Animal Studies

Ott et al[134] were the first to coinject skeletal myoblasts and BM-MNCs into the myocardium of rats 7 days post-infarction. Eight weeks later, the combination group demonstrated improved EF/LVEDD/LV end-diastolic volume, myotube formation, and retention of BM-MNCs.[134] Intramyocardial injection of the same combination of cells into canines 2 weeks post-infarction yielded similar results compared with either cell group individually.[135] Quijada et al[136] created a fusion between murine MSCs and cardiac progenitor cells, termed cardiac chimeras (CC). They tested the efficacy of CCs in a mouse AMI model compared with the combination of CSC/MSCs or each cell type alone. Four weeks post-injection, CC-treated animals showed enhancement of wall thickness. Cardiac function was improved in the CC group at 6 weeks and in the MSC/CSC group at 18 weeks. Infarct size, engraftment, and persistent engraftment were noted in the CC group when compared with MSC/CSC.[136]

Large Animal Studies

The combination of MSCs and CSCs has been studied in swine. Intramyocardial injection of human MSC and human CSCs was administered to immunosuppressed swine 14 days post-MI. This combination produced a 2-fold reduction in scar size, 7-fold enhanced engraftment, improved LV compliance and contractility when compared with individual cell types 4 weeks later (Figure 2). The individual cell types produced significant improvements compared with placebo-treated animals.[35] In a chronic ischemic, nonimmunosuppressed swine model, autologous MSCs±CSCs were administered 3 months post-MI. EF, stroke volume, cardiac output, and diastolic strain were all improved in the combination group when compared with MSCs alone. Both cell-treated groups significantly improved scar size, wall motion, and viable tissue when compared with placebo.[59] A similar study using allogeneic MSCs and CSCs again showed that the cell combination produced greater improvements in cardiac structure and function[137] at least in part by increasing cell proliferation within the myocardium.[59,137]



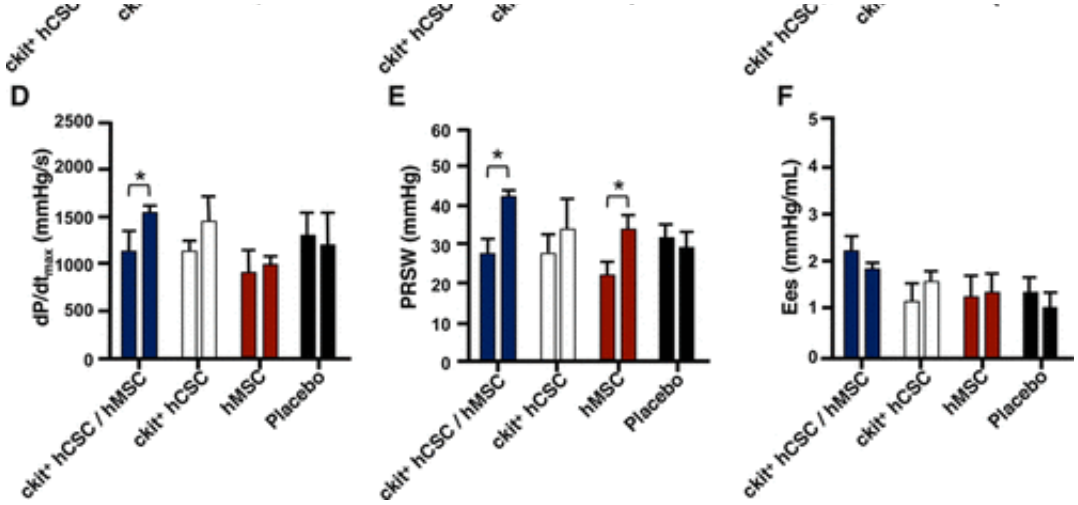


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Figure 2. Combination cardiac stem cell (CSC)/mesenchymal stem cell (MSC). Preload, afterload, and contractility changes after human CSCs (hCSC) and human MSCs (hMSCs). **A**, Left ventricular end-diastolic pressure (LVEDP) and (**B**) end-diastolic volume (EDV) and afterload measured by (**C**) arterial elastance (Ea). Combination hCSC/hMSC therapy improved contractility as measured by the (**D**) maximal rate of pressure change during systole (dP/dtmax) and (**E**) preload recruitable stroke work (PRSW), a preload-independent measure of stroke work. There was no change in (**F**) systolic elastance (Ees), in any of the groups. All graphs show pre-injection (2 weeks post–myocardial infarction [MI]) vs 4-week postinjection values. Graphs represent mean±SEM. *$P<0.05$. Reprinted from Williams et al[35] with permission. Copyright ©2013, the American Heart Association.

Paracrine Effects

Considering the reported limited engraftment of transplanted cells, the idea that stem cells secrete factors that activate endogenous cells is particularly attractive.[138] This secretome is frequently enhanced by pre-incubation under stressful conditions, such as hypoxia further supports the paracrine hypothesis. Table lists some of the potential molecular agents responsible for the paracrine effects. It is likely that a variety of different factors contribute to the regenerative and protective effects. The recruitment of resident stem cells from cardiac tissue or an increased homing of circulating progenitor cells derived from BM is likely enhanced by secreted factors.

Cell-Free Medium

Studying stem cell–conditioned medium will help identify the secretome.[139,140] For a pig

Studying stem cell–conditioned medium will help identify the secretome.[138,140] For a pig study, MSCs derived from human ESCs were cultured in serum-free conditions and the cell medium was collected and applied intravenously.[139] Three weeks post-MI, pigs treated with conditioned medium showed reduced infarct size and preserved cardiac function compared with the control group treated with nonconditioned medium. Capillary density was higher, and collagen deposition in border and remote zones was lower in animals receiving the conditioned medium. As mentioned above, (some of) the cardioprotective effects of EPCs seem to be mediated by IGF-1.[124] Percutaneous intramyocardial injection of the secretome from apoptotic peripheral blood mononuclear cells decreased infarct size and infarct transmurality measured by cardiac magnetic resonance imaging in a pig model of chronic LV dysfunction.[141]

Extracellular Vesicles/Exosomes

Extracellular vesicles (EVs)/exosomes are membrane-bound structures containing a variety of factors including short noncoding nucleic acids microRNAs and proteins. EVs/exosomes have sparked intense interest as the potential mediators of cell-based paracrine effects.[142–144] Exosomes purified from MSC-conditioned medium provide cardioprotection in an MI mouse model.[145] CSC-derived exosomes recapitulate the major effects of CSCs in both AMI and chronic MI mouse models.[146] Adamiak et al[147] recently characterized murine iPSC-derived EVs which were enriched in miRNAs and proteins with proangiogenic and cytoprotective properties. Importantly, iPSC-derived EVs provided equal or greater therapeutic efficacy as iPSCs without the potential tumor formation.[147] As described above, CDC-derived exosomes produced equivalent levels of cardiac repair as did CDCs in a porcine model.[108] These exciting results await comprehensive clinical evaluations.

Delivery Routes

While the search for the optimal cell type continues, so does the pursuit of the optimal delivery method. The most common routes include intracoronary, intravenous, and intramyocardial (transendocardial/transepicardial). Despite the various delivery methods, cellular retention remains low.[33]

Intracoronary delivery of cells is the most used approach in the clinical setting.[148] Relatively inexpensive and well tolerated, this approach can be used during an acute ischemic event combined with coronary intervention.[149] Large animal studies on canines and swine have proven the efficacy of this method.[150,151] However, arterial obstruction may pose a risk with high cell doses, and its application is limited in the chronic ischemia setting, secondary to the diffuse nature of the disease.[152] Intravenous delivery is noninvasive and well tolerated in a swine model,[153] yet fairly inefficient, as most of the

noninvasive and well tolerated in a swine model, [illegible] yet fairly inefficient, as most of the cells are lost to other organs.[55]

When accompanied by cardiac mapping, the transendocardial approach, although invasive, delivers cells most accurately.[154,155] Multiple swine studies have demonstrated improved cardiac function and reduced infarct size with this approach.[57–59,61,137] Caution should be taken in the elderly with thinner myocardium as there have been reports of ventricular perforation and cell clumping in areas of profound ischemia.[156]

The transepicardial method requires invasive thoracotomy, but is commonly used preclinically.[33] Under direct visualization, cells can be precisely injected into viable tissue surrounding the scarred area. Any perforations or hemorrhage can be controlled immediately. This delivery method produced improvements in EF, LV end-diastolic volume, and LVESV compared with placebo in a sheep model 8 weeks post-injection.[157] Other large animal studies have reported the benefits of this approach.[35,64] Drawbacks include prolonged postoperative recovery, arrhythmias, embolization, and leakage of cells from the injected sites as reported in a swine study.[148]

Patches/Biomaterials

As discussed above, generally <10% of injected cells are available at the site of injury within a few hours or days after delivery, and few cells actively engraft in the affected tissue. This rapid cell loss represents a major issue not only by limiting engraftment but also for maintaining paracrine effects, many of which function only locally. Scaffolds/patches have been constructed from various biomaterials (gelatin, Matrigel, and collagen) to mimic the extracellular matrix lost secondary to MI and help retain transplanted cells. These biomaterials include epicardial patches, self-assembling nanofibers, cell sheets, or injected gels which can be mixed with various cell types and placed on the infarcted region.[158,159] Biomaterials need to fulfill many (sometimes contradictory) criteria to be effective, including biocompatibility, biodegradability, provide mechanical support, be an appropriate thickness, and allow for precise placement.[160] The advent of 3-dimensional printing has expanded the availability and diversity of biomaterials allowing for cell integration, vascularization, and thicker structures.[161]

Conclusions and Future Directions

Ranging from in vitro discoveries of the activation and differentiation of stem cells to large animal models mimicking human heart anatomy to culminating in clinical trials, stem cell therapy has been both promising and progressive.[33] Here, we discussed promising preclinical studies using a variety of stem cells introduced in different ways to treat a diverse assortment of animals with cardiac diseases (Figure 3). These preclinical results

show that many types of cells are therapeutic, but we must continue to study more cell types and use novel approaches, including combining different types of stem cells, reinjecting cells, improving retention, and perhaps using the cell secretome rather than the cell itself.

As with all models, there are caveats associated with current preclinical studies. (1) The age of the animal is a crucial factor, with young healthy animals used for most studies. However, in humans, HF is primarily associated with aging.[3] (2) The uniformity of animals of a given strain and lack of comorbidities does not match human heterogeneity. (3) A lack of standardized protocols with consistent end points and outcome parameters. What is needed are multicenter randomized studies with a centralized core laboratory and blinded analyses, as suggested by the National Heart, Lung and Blood Institute-sponsored CAESAR (Consortium for Preclinical Assessment of Cardioprotective Therapies) consortium[162] and the Working Group on Cellular Biology of the Heart of the European Society of Cardiology.[163] (4) The different routes of injection influence therapeutic efficacy.[48] Despite these caveats, critical interpretation of preclinical models is necessary to move regenerative medicine forward.

MSCs have been the most studied cell type. They are widespread, immunomodulatory, and immunoevasive and secrete exosomes and growth factors. Despite their demonstrated benefits in acute, chronic, and DCM, complete recovery using MSCs alone has not occurred. Newer sources of stem cells, including UC/Wharton's jelly, have shown potential and a different transcriptome.[81] Stem cells isolated from the heart, including c-kit$^+$ CSCs and cardiospheres improve cardiac function and scar size in animal models. Pluripotent cells and their derivatives have similarly shown some promise.

The combination of MSCs and c-kit$^+$ CSCs has proven efficacious in large animal studies[35,59,137] and is being translated to the clinical arena (in the Transendocardial Autologous Cells [hMSC] or [hMSC] and [hCSC] in Ischemic Heart Failure Trial [TAC-HFT-II]; NCT02503280). Repeated MSC injections can be more effective than a single administration,[164] whereas Terrovitis et al[165] followed the transepicardial injection of CSCs with a fibrin-based sealant in rats to enhance cellular retention. Cell-free systems, particularly microvesicles/exosomes, with their collection of growth factors, microRNAs, etc, may represent the next frontier either alone or in combination with cells. We anticipate that novel preclinical approaches will provide more effective treatments and will pave the way for future clinical trials. The current standard of care for HF is to prescribe a cocktail of medications for patients to take for the remainder of their lives. The anticipated ability of stem cells to repair a compromised heart means that patients may reduce their medications and live active and healthy lives.

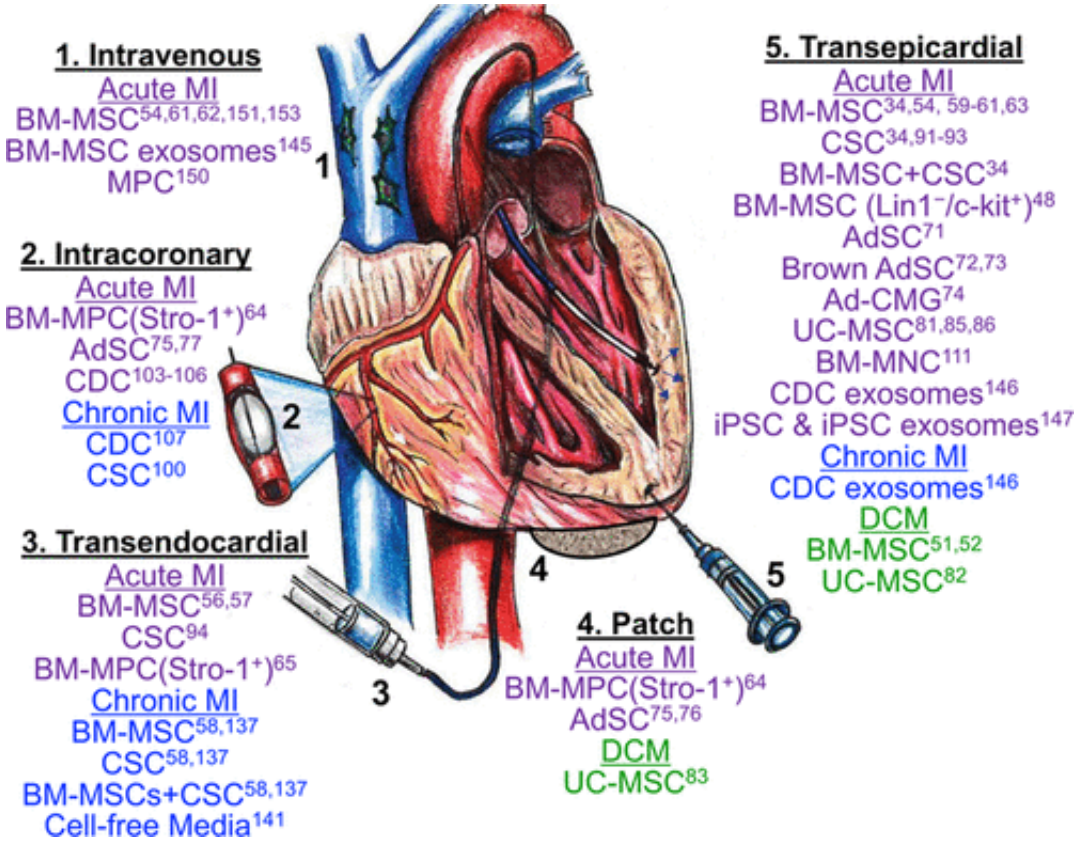

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Figure 3. Different administration routes and cell types for the treatment of heart disease. The cell types listed under each delivery method refer only to those referenced (superscripted number) in this review. AdSC indicates adipose-derived stem cell; BM, bone marrow; CDC, cardiosphere-derived cell; CMG, cardiomyogenic cell; CSC, cardiac stem cell; DCM, dilated cardiomyopathy; iPSC, induced pluripotent stem cell; MI, myocardial infarction; MNC, mononuclear cell; MSC, mesenchymal stem cell; and UC, umbilical cord. Adapted from Golpanian et al[166] with permission. Copyright ©2016, the American Physiological Society.

Nonstandard Abbreviations and Acronyms

5-aza	**5-azacytidine**
AdSC	**adipose-derived stem cells**

AdSC	
AMI	acute myocardial infarction
BM	bone marrow
BM-MNC	bone marrow mononuclear cell
BM-MSC	bone marrow-derived mesenchymal stem cell
CC	cardiac chimeras
CDC	cardiosphere-derived cell
CSC	cardiac stem cell
DCM	dilated cardiomyopathy
eGFP	enhanced green fluorescent protein
EPC	endothelial progenitor cell
ESC	embryonic stem cell
EV	extracellular vesicle

EV	[illegible]
HF	**heart failure**
IGF-1	**insulin-like growth factor-1**
iPSC	**induced pluripotent stem cell**
LAD	**left anterior descending**
Lin	**lineage**
LVEF	**left ventricular ejection fraction**
MI	**myocardial infarction**
MSC	**mesenchymal stem cell**
TACTICS	**Transnational Alliance for Regenerative Therapies in Cardiovascular Syndromes**
TGF-β1	**transforming growth factor-β1**
TNF-α	**tumor necrosis factor-α**

UC	**umbilical cord**
VEGF	**vascular endothelial growth factor**

Disclosures

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Footnotes

*These authors contributed equally to this article.

This article is Chapter 4 in an ongoing series on Cardiovascular Regenerative and Reparative Medicine. An overview of this series is available at http://circres.ahajournals.org/content/122/2/199.

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