Stem Cell Therapy for Myocardial Infarction: Challenges and Prospects

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Abstract

Myocardial infarction causes death worldwide with the greatest incidence being in the United States. Although there have been many advances in myocardial re-perfusion strategies and novel pharmacological approaches, therapies for treating acute and chronic myocardial ischemic damage remain limited. This means that no currently available heart failure treatment has demonstrated an ability to generate new muscle tissue within the scarred regions of the heart. Stem cell, however, offers new hope to patients who have otherwise limited choices. Therefore, this review aims at exploring the use and peculiarities of stem cell therapy for myocardial infarction. But the success of stem cell therapy for clinical use needs the validation of several issues ranging from selection of appropriate stem cells, routes of transfer, establishment of conducive trans-differentiation milieu with associated cytokines, means to evaluate/track response to cell therapy to compliance with regulatory and ethical issues besides addressing biological and technical issues surrounding stem cell therapy.

Keywords: Heart; Myocardial infarction; Stem cell; Therapy

Abbreviations: ACC: American College of Medicine; ACE: Angiotensin Converting Enzyme; ADSCs: Adipose Derived Stem Cells; AHA: American Health Association; AMI: Acute Myocardial Infarction; BMGPs: Bone Morphogenetic Proteins; BMSCs: Bone Marrow Derived Stem Cells; CD: Cluster of Differentiation; EPC: Endothelial Progenitor Cell; FGFs: Fibroblast Growth Factors; HSCs: Hematopoietic Stem Cells; ICD: Implantable Cardioverter-Defibrillator; LV: Left Ventricle; LVEF: Left Ventricle Ejection Fraction; MI: Myocardial Infarction; MRI: Magnetic Resonance Imaging; MSCs: Mesenchymal Stem Cells; PET: Positron Emission Tomography; SDF1: Stromal Cell Derived Factor 1; SPECT: Single Photon Emission Computed Tomography; VEGF: Vascular Endothelial Growth Factors

Introduction

Myocardial infarction (MI) is a main cause of mortality and morbidity in Western societies [1]. In USA the estimated annual incidence of MI is 610000 new attacks and 325000 recurrent attacks [2]. The American Heart Association (AHA) recently created a new set of ‘Impact Goals’ for the current decade. The aim, by 2020, is to improve the cardiovascular health of all Americans by 20%, while reducing deaths from cardiovascular disease and stroke by 20% [3].

Although there have been many advances in myocardial reperfusion strategies and novel pharmacological approaches, therapies for treating acute and chronic myocardial ischemic damage remain limited. That means, no currently available heart failure treatment has demonstrated an ability to generate new muscle tissue within the scarred regions of a heart. Stem cell therapy, however, offers new hope to patients who have otherwise limited choices [4].

In recent years, the understanding that regenerative processes exist at the level of the myocardium has placed stem cell research at center stage in cardiology. Through cellular therapies, the concept of "growing" heart muscle and vascular tissue and manipulating the myocardial cellular environment has revolutionized the approach to treating heart disease. Unfortunately, however, the vast field of possibilities opened by stem cell therapy has frequently given rise to more questions than answers [5]. Therefore, this review aims at exploring the peculiarities of stem cell therapy for MI besides outlining the limitations of stem cell therapy for MI with respect to ethical, biological and technical issues.

Rationale for Stem Cell Therapeutic Approaches

Attributes of stem cells

Stem cells are unspecialized cells that have two defining properties; the ability to self-renew and the ability to differentiate into other cell types. The biological principle that underlies stem cell therapy is tissue-directed differentiation. For example, adult stem cells isolated from liver tissue and re-injected into liver become hepatocytes, whereas the same cells injected into myocardium become myocytes. Furthermore, stem cells have been engrafted in to a broad spectrum of tissues, including regenerating bone, neural tissue, dystrophic skeletal muscle, and injured skeletal muscle [6].

Integration of stem cells with viable myocardium

Normal embryologic development of the myocardium (not to mention the whole heart, with its valve and complex architecture) depends on a series of coordinated, sequential, irreversible events (cellular differentiation, genetic expression, migration, and autocrine secretion) that are hard to imagine as being reproducible in the adult heart under normal conditions. Although transplanting stem cells will indeed develop into myocardial cells, this approach can hardly solve the problem of effective myocardial regrowth throughout the entire infarcted area. Stem cell migration into an environment so different from the embryonic cardiac jelly seems quite unlikely; at the same time, satisfactory spatial and functional integration of the new myocytes into the remnant of the viable myocardium would likely constitute a formidable challenge [7].

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Recent observations in the adult heart have suggested that adult cardiac and non-cardiac stem cells, such as those obtained from the bone marrow, brain, skeletal muscle, adipose tissue, liver, or peripheral blood may become cardiomyocytes after undergoing natural migration or experimental transplantation into the heart. This evidence indicates that the presence of such cells in the adult extracellular cardiac environment (which may need to be ischemic or damaged for this phenomenon to occur) induces the maturation of cardiac phenotypes [7].

The pivotal finding by Ashahara and colleagues that postnatal vasculogenesis exists (i.e. that stem cells contribute directly to the formation of new blood vessels in adults) provided new insights into mechanisms of cardiac repair. In the adult, revascularization does not rely exclusively on angiogenesis (sprouting from preexisting blood vessels). Furthermore, endothelial progenitor cells (EPCs) that originate in the bone marrow play a role in vasculogenesis (physiological and pathological) and circulate in adult peripheral blood. The intriguing observation in heart transplant patients that putative stem cells and progenitor cells from a recipient were present in the transplanted heart further supports the notion of ongoing regenerative and reparative mechanism mediated by circulating stem cells from the bone marrow [5].

Sources of stem cells for cardiac repair

Over the past decade, several indications using a variety of different types of stem cells have emerged including embryonic stem, adipose derived stem cells, peripheral blood stem cells and skeletal myoblasts for use in acute MI, chronic ischemia, and chronic heart failure. In addition to cellular therapy for the existing heart, some groups are attempting to create a bioartificial heart using cardiac or endothelial cells [4].

The recent discovery of cardiac stem cells obtained directly from adult cardiac tissue could lead to new treatments for heart failure patients [8]. It is believed that these cells are inherently programmed to reconstitute cardiac tissue and play a role in the clinical benefit observed in other stem cell trials. The proteins secreted after stem cell therapy may promote regeneration in a paracrine effect which is related to the inherent cardiac stem cells [9]. These cells have only recently been introduced into the field and there are still several obstacles to overcome prior to advancing his platform to the clinic. Cardiac stem cells have been difficult to isolate and to expand ex vivo into meaningful numbers without losing differentiation potential and several groups are exploring ways to improve this cell population [10].

Bone marrow derived stem cells (BMSCs) have been utilized in variety of indications within the heart. These cells have primarily been to assist in the angiogenesis process and to assist in the revascularization of hibernating tissue. Typical clinical applications have been in acute MI and myocardial ischemia. Pompilio et al. (Arterioxyte, Inc.) demonstrated long term clinical and perfusion improvements in the absence of adverse events when injecting bone marrow derived stem cells into patients with myocardial ischemia [11].

Adipose tissue consists of adipocytes and a mononuclear cell fraction that contains a mesenchymal stem cell population. These cells are very similar in nature to bone marrow derived stem cells and in some cases have advantages over bone marrow derived stem cells. In one study by Zhang et al., adipose derived stem cells (ADSCs) exhibited a higher percentage of differentiating into cardiomyocytes when compared to bone marrow mesenchymal stem cells (MSCs). These results along with an advantage in tissue content, homology, growth and differentiation rate indicate that ADSC may be better suited for cellular cardiomyoplasty than MSCs [4].

There has been some research in the use of peripheral blood and collection of stem cells for use in cardiovascular diseases. Baxter has recently completed a phase II trial of 150 patients to assess the safety and efficacy of CD34+ cells in patients with chronic myocardial ischemia. Patients receive granulocyte colony stimulating factor to mobilize the hematopoietic (blood-forming) CD34+ cells from their bone marrow to their bloodstream. Then, a cell separation system collects a mononuclear cell preparation rich in CD34+ stem cells from the patient's bloodstream and separates the cells using magnetic for use in the heart [12].

Skeletal myoblasts have been studied in over 2000 animals, 350 patients and was one of the first stem cells to enter into the clinical for cardiovascular diseases. A variety of groups have studied this platform with a variety of trial designs. The human body cannot, without medical assistance, repopulate regions of scar tissue within the heart with functioning muscle. Unlike other cells that have the capacity to fuse with other myoblasts are designed to improve cardiac function by populating regions of scar tissue. Myoblasts, which are obtained from a biopsy of the thigh, are precursors to muscle cells that have the capacity to fuse with other myoblasts or with damaged muscle fibers to regenerate skeletal muscle. When injected into scar tissue within the heart wall myoblasts have been shown to express various proteins that are important components of contractile function. The use of myoblasts obtained from a patient's own body helps to avoid certain challenges currently faced by other cell-based clinical therapies intended to be used for the treatment of chronic heart damage including tissue rejection and instances of the cells differentiating into cells other than muscle [4].

Embryonic stem cells may also have a potential role in cell therapy. Currently, however, these cells are available only in limited numbers, and their therapeutic use would likely introduce ethical and regulatory dilemmas as well as the risk of allograft immunologic reactions. Until now, it has not been possible to promote, in an in vitro culture, the development of layer of pure cardiomyocyte lineages derived from embryonic cells [7].

Though stem cells of various origins that show plasticity to cardiomyocytes are identified, this paper focuses more on study trial principally on BMSCs as prototypes. In a series of reports, it has been suggested that adult BMSCs has been established by identifying specific cell surface markers or by fluorescence in situ hybridization identification of Y-positive nuclei in donor-derived cells that have acquired the capacity to synthesize specific protein in regenerating tissues.

**Stem Cells Repopulation and Mechanisms of Repair**

**Technique for stem cell administration**

Administration of different types of progenitor cells by means of endovascular (intravenous or intracoronary) injection has been attempted in pilot studies, with promising early results. Readily available angioplasty catheters can be used for the intracoronary route but may entail a risk of microvascular obliteration and of poor therapeutic efficiency if the stem cells are to cross the coronary arteries. Bone marrow-derived stem cells appear to migrate through the arterial or capillary wall better than do skeletal myoblasts. The vascular approach seems generally less promising than direct intramural injection into the target myocardium, either surgically (via the epicardial approach) or by catheter via the endocardial approach [7].

Although the ideal route for administering stem cells is still yet to be determined, it may be important to take certain factors into
Mechanisms of repair

Current evidence favors the conclusion that embryonic stem cells have multiple possible pathways of differentiation and that the embryonic interstitial matrix normally carries the messengers and inductors of final choice (which are not yet well known). Experimental embryology data have recently shown that extracardiac mesoderm does not normally produce heart tissue but can do so when transplanted into a specific cardiac extracellular medium. Likewise, extracardiac posterior mesoderm does not normally produce heart tissue but will express a cardiac phenotype when treated with extracellular regulators such as BMPs, FGFs, Wnt, and Dickkopf-1. This phenomenon suggests that the embryonic cardiac jelly, on extracellular matrix, is a critical carrier of signaling instructions and enables the cellular migration necessary for the acquisition of proper intercellular spatial and functional organization. For the formation of definitive cardiac chambers, myocardial specialization (into atria, ventricular, and conduction elements) is required. This necessitates the influence of several genes, such as those that encode peptide atria natriuretic factor; Hand 1, cited 1, and Irx 1/2/3; gap junction protein cannikins 40 and 43; the secreted peptide atria natriuretic factor; and the cytoskeleton protein Chisel [7].

It has been shown that stem cell homing molecules Stromal-cell Derived factor-1 (SDF-1) is transiently expressed following MI, and that re-establishment of this homing factors in myocardial tissue months after MI is sufficient to induce stem cell homing, vasculogenesis and recovery of myocardial function. SDF-1 is a family of CXC chemokines, and its receptor is CXCR4. The SDF-1/CXCR4 pathway is critical during embryogenesis for hematopoietic, vascular development, and cardiac development. It has been reported that 1) cells expressing markers of hematopoietic stem cells or EPCs express CXCR4; 2) vascular endothelial growth factor (VEGF) induces the expression of VEGF and induces angiogenesis in vivo [13-17]; SDF-1 and its receptor CXCR4 are crucial for bone marrow retention of hematopoietic stem cells and are involved in cardiogenesis and recruitment of endothelial progenitor cells to sites of ischemic tissue [18].

The mechanisms by which BMC therapy may improve cardiac function are still debated and not entirely clear. Whereas initial experimental studies had suggested a rapid transdifferentiation of BMCs (c-kit, lineage-) into cardiomyocytes after cardiac injection post-MI, probably inspired by the concept of a high stem cell plasticity post-MI, probably inspired by the concept of a high stem cell plasticity, the injections sites can be identified using contrast agents. Furthermore, the injections sites can be identified using contrast agents. The ST-elevation myocardial infarction (STEMI) is a condition where the blood supply to the heart muscle is severely reduced due to a blockage in one of the coronary arteries. This can lead to irreparable damage to the heart muscle and can be life-threatening if not treated promptly. The main objective of STEMI treatment is to re-establish blood flow to the heart muscle as quickly as possible, which can be achieved through various interventions such as percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). The success of these treatments depends on the speed and efficiency of the intervention, as delayed reperfusion can lead to further tissue damage and potential complications. Therefore, it is crucial to develop effective strategies and technologies for monitoring the fate and function of transplanted stem cells, particularly in the context of early-stage cardiovascular repair, where timely and reliable information is essential for optimizing treatment outcomes. This involves the use of advanced imaging techniques such as magnetic resonance imaging (MRI), positron emission tomography (PET), and optical imaging, which allow for the visualization of stem cell distribution, viability, and function over time. These technologies enable researchers and clinicians to assess the efficacy of stem cell therapies and inform decision-making regarding patient care. The integration of multidisciplinary expertise across imaging sciences, stem cell biology, and cardiac regeneration is essential for advancing the field and improving clinical outcomes.
which results in cell engraftment, may play a key role in the success of
cell therapy. After acute ischemic myocardial injury, serum stoma cell
derived factor-1 levels rise significantly, and this chemokine appears to
be one key homing signal that regulates homing of stem and progenitor
cells to the ischemic myocardium. In patients with chronic ischemic
cardiomyopathy, however, local homing signals may not be as intense
as in the early post-infarction phase, and therefore the coronary route
might not be optimal for cell engraftment [13].

Bone marrow derived stem cells work best in an acute setting or in
hibernating tissue mainly due to the fundamental characteristics of
mesenchymal stem cells. Bone marrow derived mesenchymal stem cells
are medium-dependent and tend to acquire the characteristics of
the cells they are in contact with. For this reason, these cells are not
appropriate for the scar tissue of a chronic myocardial infarct (i.e., into
the fibrotic area, because they would tend toward differentiating into
more fibrosis) [16].

Cytori therapeutics has recently completed enrollment in study
to investigate adipose derived stem cells in chronic heart disease. The
phase I PRECISE trial was carried out at several centers in Europe with
enrollment of 27 patients. The independent data safety and monitoring
board had not identified any safety concerns and six month results are
expected in the first half of 2010 [14]. Cytori is also currently recruiting
for a phase I study at two centers in Europe to establish the safety and
feasibility of Adipose derived stem cells in patients with AMI [15].

Constraints and Options

Ethical issues

Though embryonic stem cells have also a potential role in cell
therapy, these cells currently are available only in limited numbers,
and their therapeutic use would likely introduce ethical and regulatory
dilemmas as well as the risk of allograft immunologic reactions [7].

Biology of senescence

Myocardial infarction is primarily a disease of older persons,
and the senescent myocardium may differ biologically from the
myocardium of young persons and from that of the small adult
animals typically used in initial stem cell experiments. In particular,
the cells (myocytes) them self and the intercellular messaging milieu
in the interstitial space may be profoundly different under each clinical
condition. Nadal-Ginard et al. [22] recently characterized the senescent
myocardium by the predominance of large myofibres (volume >90,000
mm3) expressing p16INK4, a marker of cellular aging and increased
apoptosis. Most likely, the molecular signals produced by such cells
and their extracellular environment are not as favorable for stem cell
differentiation, migration, and integration as are the signals present
in younger hearts. These conditions need to be further characterized,
because they might allow physicians to modify the environment,
making it more conducive to successful stem cell treatment [7].

Miscellaneous factors

In contrast to oral medication pharmacological agents, BMC
therapy is an invasive treatment option. Bone marrow aspiration is
usually performed under local anesthesia and is generally well tolerated.
However, the procedure is without doubt a strain for the AMI patient
and stent thrombosis has been described. Alternatively, the aspiration
procedure can be performed under a brief general anesthesia. Both
this procedure and the repeated left-sided heart catheterization for cell
administration expose the patient to the risk of possible procedure-
related complications. Coronary artery dissection has been reported
after BMC administration. Furthermore, there has been concern about
increased rate of restenosis after BMC therapy, although this has not
been reported after injection of unfractioned cells in the absence of
bone marrow mobilizing agents. Another aspect s that MBC therapy
is unlikely to transfer to a clinically important improvement in patient
outcomes and that it probably not outweighs the cost, effort, and risks
of a large-scale clinical trial [21].

Despite several limitations, there are alternative ways to acknowledge
the potential of BMC therapy. Considering the well-known limitations
of the methods that have been used, it is amazing that there seems to be
any effect of this treatment. First, we have not identified the cell (s) with
a possible regenerative effect. Second, we do not know the mechanism
of action. Third, cell numbers that have been delivered are probably too
low to expect clinically relevant myocardial regeneration [23]. Fourth,
few cells remain in the heart regardless of administration mode [24],
and finally, most of the few cells that remain in the heart die shortly
after delivery [25] of AMI patients. Further research will probably
develop techniques that will overcome these obstacles. It is possible to
deduce that, the field is not yet ready for large-scale trial, and it will be
better to use resources on more basic research and continue small to
intermediate sized, well-designed clinical trials.

Conclusion

While the initially perceived rapid chance for a complete cardiac
repair by stem/progenitor cell therapy after MI has generated high
expectations, now the potential of this therapy needs to be carefully
defined by addressing important remaining questions, including the
optimal cell types and preconditioning, the timing and dosing cells to
be seed, how to augment the functional repair capacity of transplanted
cells, how to optimize their homing and engraftment in the heart, and
how to select the patients that may benefit most from this therapy.

Conflict of Interests

The authors declare that they have no competing interests.

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