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SPECIAL ISSUE

Cell Therapy for Myocardial Infarction

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Ischemic heart disease, particularly acute myocardial infarction (MI), is the worldwide health care problem and the leading cause of morbidity and mortality. The fundamental treatment of MI remains a major unmet medical need. Although recent tremendous advances have been made in the treatment for acute MI such as percutaneous coronary intervention (PCI) and medical and surgical therapies, myocardial cell loss after ischemia and subsequent, adverse cardiac remodeling and heart failure are demanding for new therapeutic strategy. Since the first experimental studies of adult stem cell therapy into the ischemic heart were performed in the early 1990s, the identification and potential application of stem and/or progenitor cells has triggered attempts to regenerate damaged heart tissue and cell-based therapy is a promising option for treatment of MI. In this review, we would like to discuss the pathogenesis of acute MI, current standard treatments and their limitation, clinical results of recent stem or progenitor cell therapy which have shown a favorable safety profile with modest improvement in cardiac function, and putative mechanisms of benefits.

Keywords: Myocardial infarction, Ischemic heart disease, Stem cells, Cell therapy, Regenerative medicine

Introduction

Ischemic heart disease, particularly acute myocardial infarction (MI), is the worldwide health care problem and the leading cause of morbidity and mortality (1). Myocardial cell loss after ischemia and subsequent, adverse cardiac remodeling and heart failure are demanding for new therapeutic strategy. Although recent tremendous advances have been made in the treatment for MI such as percutaneous coronary intervention (PCI) and medical and surgical therapies, myocardial cell loss after ischemia and subsequent, adverse cardiac remodeling and heart failure are demanding for new therapeutic strategy (2, 3).

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Regenerative medicine is seeking for an innovative therapeutic strategy that assures to ameliorate health and quality of life by restoring or regenerating cells, tissues or organs. Cellular therapy using stem/progenitor cells has been experimentally and clinically investigated to regenerate or repair the damaged heart (2-4). The adult heart had been believed not to have a capacity of self-regenerating cells (5, 6). In this context, over the past decade, various types of extracardiac cells such as bone marrow (BM)-derived cells, adipose-derived stem cells, skeletal myoblasts as well as embryonic stem cell-derived cardiomyocytes have been proposed as potential cell sources for cardiac cell therapy (2-4, 7-12). Experimental preclinical studies have been shown promising results for cardiac repair after acute MI; reduction of infarct size and improvement of left ventricular systolic function (13). However, cardiac differentiation of extracardiac cells remains under heavy debate (14, 15), and clinical trials, especially BM-derived cells, have shown modest or marginal benefits when transplanted into acute or chronic MI patients (16, 17).

In this review, we would like to discuss the pathophysio-

logy of acute MI, diagnosis and current conventional treatments and their limitation, clinical results of application of stem and/or progenitor cell therapy for MI, and putative mechanisms of benefits. We also discuss the open issues for future advance.

Pathophysiology of acute MI

MI is defined as an event caused by myocardial ischemia in which there is evidence of myocardial injury and/or necrosis. Most cases of MI are resulted from coronary atherosclerosis with superimposed coronary thrombosis, although non-atherogenic forms of coronary disease may cause MI (18, 19). During the progression of atherosclerotic plaque, especially which is lipid laden, an abrupt transition would occur, characterized by plaque disruption (20). When plaque disruption occurs, thrombogenic substances are exposed, and the lumen of coronary artery becomes obstructed by a combination of platelet aggregates, fibrin, and red blood cells that produce thrombus filling of the infarct-related artery (21). Such occlusive thrombi lead to a zone of necrosis in the ventricular wall.

The pathology of MI is defined as cardiomyocyte cell death as a consequence of prolonged ischemia. Characteristic findings include coagulation necrosis and contraction band necrosis, often with patchy areas of myocytolysis at the periphery of the infarct. During the acute phase of MI, the majority of cardiomyocyte loss in the infarct zone occurs via coagulation necrosis and proceeds to inflammation and phagocytosis of necrotic myocytes, and repair as fibrotic scar formation.

Diagnosis of acute MI

The clinical diagnosis of MI requires an integrated assessment of the history with combination of (in)direct evidence of myocardial necrosis using biochemical, electrocardiographic, and imaging modalities (22). In 2007, the Joint Task Force of the European Society of Cardiology, American College of Cardiology Foundation, the American Heart Association, and the World Health Federation (ESC/ACCF/AHA/WHF) refined the old criteria and defined acute MI as a clinical event consequent to the death of cardiomyocytes (myocardial necrosis) that is caused by ischemia (23). The diagnosis of MI is required the followings: Typical rise and/or gradual fall (troponin) or more rapid rise and fall (CK-MB) of biochemical markers of myocardial necrosis with at least one of the following (24, 25): (1) Ischemic symptoms, (2) Development of pathologic Q waves on the electrocardiography (ECG), (3) ECG changes indicative of ischemia (ST segment elevation or depression), (4) Imaging evidence of new loss of viable myocardium or a new regional wall motion abnormality. Myocarditis or trauma can cause cell death and myocardial necrosis but these cases are not defines as MI.

Current treatment of acute MI and limitations

The management of the patient MI has been emphasized on prompt diagnosis, because the beneficial effects of early reperfusion therapy are the greatest when performed soon after the onset of symptoms after hospital presentation. A number of hospitals usually apply checklists, or critical pathways to screen patients with a suspected MI, which combine diagnostic evaluation such as ECG and serum biomarkers with therapeutic interventions such as aspirin, beta blockers and antithrombotic therapy. When MI is diagnosed, early reperfusion therapy for occluded coronary arteries is the major therapeutic strategy. Reperfusion can be obtained mechanical or biochemical measures; percutaneous coronary intervention (PCI) or fibrinolytic therapy (24-26). However, there is a very narrow therapeutic window to prevent myocardial necrosis. Usually 3 to 6 hours after MI onset, the efficacy of reperfusion therapy and the extent of salvaged myocardium by reperfusion is abruptly declined, and 12 hours after MI, the therapeutic benefit of reperfusion is marginal, so cardiologists believe that “Time is myocardium” as the longstanding axiom (27).

Pharmacological treatments including antiplatelet agents, beta blockers, ACE inhibitors and angiotensin II receptor blockers and statin are also important (24, 25, 28). Taken together, recent progress in the management of patients with an acute MI has led to a decline morbidity and mortality. Nevertheless, survivors of an MI still face a substantial excess risk of mortality as well as further cardiovascular events including angina, recurrent MI and heart failure.

The critical limit of current standard treatments for MI is that the damaged cardiac muscles and vessels could not be regenerated. The heart has been considered as a static organ and the capacity of the hearts to regenerate functional myocardium is extremely limited or absent. Not surprisingly, it has been thought that the prognosis of MI is dismal while the long-term survival rate of infarct patients was even worse than that of cancer patients. Therefore, the demand for the regeneration of cardiac muscle and vessel is tremendous.

Table 1. Clinical trial for acute MI using bone marrow-derived cells

Study name	Enrolled patient No.	Cell type	Delivery route	Myocardial function (LVEF change %)	Infarct size (change %)	Reference
MAGIC-Cell I	27	G-CSF mobilized PB-MNCs	Intracoronary	(+) 6.4%	(−) 6.3%	29
MAGIC-Cell III-DES	56	G-CSF mobilized PB-MNCs	Intracoronary	(+) 5.2%	•	34
Strauer et al.	20	BM-MNCs	Intracoronary	(+) 1.0%	(−) 13.0%	30
Bartunek et al.	35	BM-MNCs	Intracoronary	(+) 3.1%	(−) 4.9%	31
BOOST	60	BM-MNCs	Intracoronary	(+) 2.8%	•	32, 41
Janssens et al.	67	BM-MNCs	Intracoronary	(+) 1.1%	•	33
ASTAMI	100	BM-MNCs	Intracoronary	(+) 1.4%	(−) 3.2%	35, 44
REPAIR-AMI	204	BM-MNCs	Intracoronary	(+) 2.5%	•	36, 42, 43
TCT-STAMI	20	BM-MNCs	Intracoronary	(+) 6.7%	(−) 5.0%	37
Meluzin et al.	66	BM-MNCs	Intracoronary	(+) 2.0%	(−) 1.0%	38
Zhan-Quan et al.	70	BM-MNCs	Intracoronary	(+) 5.5%	•	39

BM-MNCs: bone marrow-mononuclear cells; PB-MNCs: peripheral blood-mononuclear cells; LVEF: left ventricular ejection fraction.

Application of stem or progenitor cell therapy for MI

Since 2001, more than 1,000 MI patients have received stem/progenitor cell therapy.

Clinical trials may be classified by applied cell types and delivery routes. A variety of cells have been tested experimentally. At present, majority of trials have primarily used autologous cells, especially, BM cells or mobilized peripheral blood cells, largely due to safe profiles of infused cells and accumulated clinical experience of BM reconstitution or transplantation in patients. Regarding the route of delivery, in the clinical setting of MI, PCI is routinely performed, so intracoronary cell infusion easily and widely applied, compared to other delivery methods such as intramyocardial direct injection. In this review, we focus on trials using BM-derived cells or mobilized peripheral blood cells from BM via intracoronary delivery. Table 1 summarizes the results from 11 clinical trials (29-39).

When clinical trials with stem cells begin, it is very important whether the methods used in the trials are safe and have the feasibility or not. In terms of the intracoronary application of stem cells in patients with acute MI, Strauser et al. first showed the safety and the effect of autologous BM stem cells in 2002 (30). Kang et al. also demonstrated that the mobilization of stem/progenitor cells from BM with G-CSF was safe and had the significant effect in improving left ventricular systolic function (29). In particular, compared to other trials using BM aspiration, they used less invasive strategy such as G-CSF-induced mobilization and apheresis to collect mononuclear cells. Interestingly, they reported the high rate of in-stent restenosis in patients who received G-CSF. After that, they showed that the use of drug-eluting stents could overcome that kind of problem with enhancing heart function (34, 40). Large randomized controlled trials have shown the beneficial effects of stem/progenitor cell therapy on the infracted myocardium in acute MI patients. In BOOST trial, 60 patients were randomized and received either intracoronary BM-mononuclear cells (BM-MNCs) or standard therapy. BM-MNC-treated group showed the improvement in left ventricular ejection fraction of 2.8%, compared to control group (32, 41). REPAIR-AMI study which enrolled 204 patients showed the improvement in left ventricular ejection fraction by 2.5% in AMI patients (36, 42, 43). However, the ASTAMI trial showed no definite effect of intracoronary infusion of BM-MNCs on left ventricular function in the patients, compared to that in the control group at 6 months after the treatment (35, 44).

In summary, BM-derived cell therapy in acute MI patients may improve left ventricular ejection fraction from 1.0% up to 6.7% and reduce infarct size by 1.0～13.0%. These results suggest the modest improvements in the pathphysiologic parameters.

Mechanisms of benefits

Currently tremendous experimental or clinical data have repeatedly demonstrated that cell-based therapy for acute MI improve cardiac function and reduce infarct size. However, the underlying mechanisms explaining these benefits remain elusive. We discuss here the possible beneficial mechanisms by which stem/progenitor cells achieve a functional improvement. Diverse types of stem cells

have been considered as source for cell therapy. Cells are classified as their origin and characterized by specific markers, genetic and proteomic differences. They also differ in their hierarchy to form one or more differentiated cell types. Embryonic stem (ES) cells are the most hierarchical cell types and differentiate into a variety of cell types and tissues, including cardiomyocytes and endothelial cells. Recently, ES cell transplantation has shown a remarkable improvement in cardiac function and structure, and the cells appear to be electrically integrated in animal models of MI and non-ischemic cardiomyopathy (45-47). However, there are ethical problems regarding by using of human embryo as well as immune rejection after transplantation in patients. To develop patient-specific stem cells, Yamanaka group generated induced pluripotent stem cells (iPSCs) with defined factors (Oct4, Sox2, Klf4 and c-Myc) from somatic cells (48-50). According to recent data, human iPSCs can differentiate into functional myocytes and regeneration of cardiac, smooth muscle and endothelial tissue in mouse models (51). Therefore, the iPSCs may provide an alternative source for the future regenerative medicine.

In contrast to ES cells or iPSCs, adult stem cells including BM-derived progenitor cells and resident cardiac stem cells, display more limited differentiation capacity. They were shown to contribute to neovascularization and cardiomyogenesis respectively. To enhance neovascularization in MI patients, it can be mediated by the physical incorporation of vascular progenitor cells into new capillaries (52) or subsequent delivery of growth factors and cytokines that enhance angiogenesis by affect on mature endothelial cells (53, 54). Humoral and paracrine factors including cytokines released from various stem/progenitor cells may favorably affect improvement of cardiac function by reducing the apoptosis of cardiomyocytes or even by activating cardiac stem cells to enhance cardio-myogenesis (55).

Mobilization strategy is also a way to improve cardiac repair. Many well-known angiogenic factors such as VEGF, angiopoietin-1, placental growth factor (PlGF) and SDF-1 were reported to increase mobilization of endothelial progenitor cells (EPCs) and enhance neovascularization (56-58). As injected BM-derived cells into infarcted myocardium could differentiate into cardiomyocytes and improve the heart regeneration effectively, hematopoietic stem cell-mobilizing factors such as G-CSF and SCF could be applied to MI patients (59). To success cell therapy, mobilized progenitor cells need to home where they are required, specifically to the injured sites. The cascade of homing is adhesion to activated endothelium, transmigration and invasion of the injured tissue. Integrins usually mediated adhesion and transmigration of progenitor cells and SDF-1 appears to be a key molecule to regulate homing of progenitor cells into ischemic tissue (60, 61).

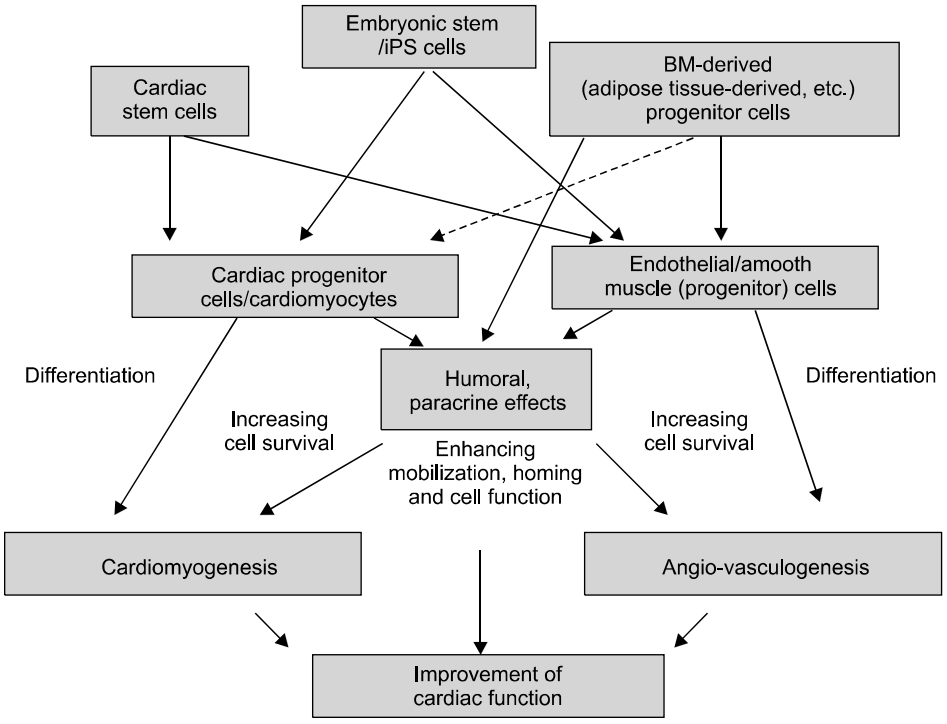

Fig. 1. Putative beneficial mechanisms of cell therapy for MI.

Fig. 1 summarizes putative beneficial mechanisms of cell therapy for MI.

Future perspective and open questions

Stem/progenitor cell research has been making rapid progress and clinical trials, especially using autologous adult stem cells, have been already reported their results and many more are undergoing. However, there are many remaining questions regarding the translational research from experimental animal studies to humans, therapeutic potentials of human adult stem/progenitor cells and clinical benefits: (1) The specific type and role of cells in may be misunderstood or overestimated. Which patients could have benefits from cell therapy has yet to be determined. The clinical setting of ischemic cardiovascular diseases and the components requiring regeneration should be considered. (2) The development of therapeutic strategies to induce both neovascularization and cardiomyogenesis are required since both processes are intimately related in successful and favorable myocardial remodeling and regeneration. (3) We need to acknowledge that not all the stem/progenitor cells possess the same therapeutic capacity and efficacy. Further investigations are needed to compare the therapeutic effects and the underlying mechanisms of different types of stem and progenitor cells, and the advantage of mixed cell therapy may need to be investigated. (4) The cell preparation, transplantation cell dose and volume, the timing of therapy, route of delivery need and clinical study design to evaluate the efficacy of cell therapy need to be determined by more sophisticated approaches. Then, the problem of lack of cellular engraftment and extensive cell death after cell transplantation should be addressed for improving therapeutic efficacy. (5) The long-term benefits the following cell therapy also has to be determined.

Overall, the transplantation of stem and/or progenitor for MI is currently not at the stage in routine clinical practice. Despite these limitations, many clinicians and experimental scientists may agree that cell-based therapy would become a potentially effective strategy for treating MI in near future.

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Potential Conflict of Interest

The authors have no conflicting financial interest.

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