

New Strategies for Myocardial Infarction Treatment

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ABSTRACT

Myocardial infarction is due to lasting and serious myocardial ischemia that leads to myocardial necrosis and cardiac remodeling, and can consequently result in heart failure. Traditional treatment for myocardial infarction includes drug therapy, thrombolytic therapy, percutaneous coronary intervention (PCI), and coronary artery bypass graft (CABG) surgery. Although these treatments can to some extent relieve the symptom of myocardial ischemia, they fail to repair the necrotic heart tissues. Myocardial regeneration is undoubtedly the best solution to the clinical problems of myocardial infarction treatment. The review briefly illustrated the pros and cons of the traditional treatments of myocardial infarction, and focused on the application of new strategies for myocardial infarction treatment using myocardial regeneration.

Key words: Myocardial infarction; Drug therapy; Thrombolytic therapy; Myocardial regeneration

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INTRODUCTION

Myocardial infarction (MI) mainly refers to ischemic myocardial necrosis. It is due to narrowing or blockage of the coronary arteries that results in drastically reduced or interrupted coronary blood flow. The lack of blood flow and oxygen to the heart muscle cause lasting severe myocardial ischemia, which eventually leading to ischemic myocardial necrosis. Myocardial infarction generally accompanied with varying degrees of impairment of ventricular function. Clinically, patients with myocardial infarction are present with systemic symptoms, such as intense and lasting chest pain, tissue necrosis, acute circulatory failure, shock, heart failure or severe cardiac arrhythmias that can cause sudden death.

TRADITIONAL TREATMENT

At present, the treatments of myocardial infarction mainly focus on the recanalization of the occluded coronary artery to restore perfusion and prevent myocardial necrosis. To do this, commonly used methods include drug therapy, thrombolytic therapy, percutaneous coronary intervention (PCI), and coronary artery bypass graft (CABG) surgery.

Drug therapies

Traditional drug therapies include angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARBs), aldosterone receptor antagonists, β -receptor blockers, and so on^[1-3]. The main purpose of these treatments is the prevention of left ventricular remodeling.

Thrombolytic therapy

Thrombolytic therapy is presently the main approach for the treatment of myocardial infarction. Principles of thrombolytic

therapy in treating acute myocardial infarction are recanalization of the occluded coronary artery and restoration of the perfusion as soon as possible.

A large number of clinical studies indicated that thrombolytic therapy that taken within 6 hours after the onset of myocardial infarction achieved the best curative effect, and the earlier treatment is started, the better the curative effect^[4].

Biochemical and clinical trials have proved that thrombosis and thrombolysis are dynamic processes occurring simultaneously. Inhibition of thrombus formation will accelerate the dissolution of blood clots^[5]. Currently, the most commonly used thrombolytic drugs are streptokinase, urokinase and tissue-type plasminogen activators^[6-8]. These thrombolytic drugs work well in the dissolution of blood clots but have some side-effects, mainly including unwanted bleeding, such as mucosal bleeding, subcutaneous bleeding, or life-threatening intracerebral hemorrhage. Nevertheless, there was only one-third of patients with myocardial infarction met the requirements for thrombolytic therapy.

Percutaneous coronary intervention

Take the limitations of thrombolytic therapy into consideration, percutaneous coronary intervention (PCI) has gradually become another choice to restore perfusion. This procedure effectively restores the blood flow and recovers the function of heart muscle by inserting a special catheter into a blood vessel and inflated at the narrowed area of the coronary artery^[9]. Compared with thrombolytic therapy, PCI removes the thrombus and the reperfusion rate after the intervention is 95% to 99%. But PCI also has some possible risks, such as bleeding or infection at the catheter insertion site, allergic reaction to the contrast dye used, blood clot within the treated blood vessel, rupture of the coronary artery, and complete closing of the coronary artery.

Coronary artery bypass grafting

Coronary artery bypass grafting (CABG) is an effective surgical treatment of coronary heart disease and myocardial ischemia, which can effectively relieve symptoms. It is also an effective method for the treatment of restenosis and acute complications in patients after PCI. Once the acute complications occur after surgery, emergency CABG will minimize myocardial damage and reduce hospital mortality and adverse events^[10]. Therefore, CABG is an important alternative or combination therapy to PCI.

Although drug therapy, thrombolytic therapy, percutaneous coronary intervention and coronary artery bypass graft surgery can to some extent prevent ventricular remodeling and relieve the symptoms of myocardial ischemia. But these treatments cannot repair the necrotic myocardial tissue and solve the fundamental problem of myocardial infarction. How to promote the regeneration of necrotic cardiomyocytes and prevent ventricular remodeling has become the key to improving the cardiac function after myocardial infarction. Therefore, in recent years, myocardial regeneration has become the hotspot of cardiovascular research. And it is also the new treatment of myocardial infarction in this review.

NEW STRATEGIES

Cardiomyocytes are traditionally considered as terminally differentiated cells. Once the cardiomyocyte is damaged, it will not be able to regenerate. In myocardial infarction, the dead myocardial cells were replaced by fibroblasts, which eventually leading to ventricular remodeling and heart failure. The discovery of stem cells makes the

regeneration of cardiomyocyte possible. Animal experiments showed that stem cell transplantation can contribute to the regeneration of cardiomyocyte and improve cardiac function^[11,12]. Some of the stem cell types are being applied in clinical trials to prove it an acceptable and applicable treatment in human^[13,14]. There are two main types of stem cells used in myocardium regeneration, pluripotent stem cells including embryonic stem cells (ESC) and induced pluripotent stem (iPS), and adult stem cells including mesenchymal stem cells, skeletal muscle myoblast cardiac stem cells (CSC) and bone marrow cells (BMC) (Figure 1).

Embryonic stem cells

Embryonic stem cells (ESC) are pluripotent cells that can differentiate into a variety of cell types, including cardiomyocyte. It has been extensively investigated for the repair of the infarcted heart. Studies in animal models have shown promising effects of embryonic stem cell-derived cardiomyocytes (ESC-CMs) treatment^[15,16]. Transplantation of human ESC-CMs in a non-human primate (NHP) model of myocardial ischemia-reperfusion showed evident remasculinization, but potential arrhythmic complications remain unsolved^[15]. Currently, there are four major reasons that hinder the clinical application of ESC: Firstly, the transplanted embryonic stem cells may differentiate into unwanted cell types in the human body. As a great many of cardiomyocytes are lost after a typical infarct^[17], complete repair of the heart requires large-scale production of ESC-CMs. While the feasibility of this large-scale committed differentiation of ESC in the human heart is not clear. Secondly, the immune system of a person may see the transplanted cells as foreign and reject them by aggressive immune response^[18]. Thirdly, stem cells may undergo a carcinogenic transformation, which means transplant recipients bear the risk for teratoma formation^[19,20]. Lastly, ethical concerns related to embryonic stem cell research limits the collection and usage of ESC^[21]. In view of the above reasons, embryonic stem cells are still limited in application.

Induced pluripotent stem cells

Induced pluripotent stem cells (iPSCs) are generated directly from patient's somatic cells by gene reprogramming, in this way, the differentiated somatic cells could convert into pluripotent stem cells. Since the transplanted iPSCs is derived from the patients, it has an important clinical advantage of avoiding immune rejection^[22]. However, it needs a longer time (16-35 days) for reprogramming of adult cells into induced pluripotent stem cells and the differentiation efficiency is very low, which greatly increases the risk of cell mutation during induction^[23]. Therefore, because of the oncogenic potential of iPSCs, larger animal and clinical trials may need before it can be translated into effective clinical treatment.

Skeletal muscle stem cells

The unipotent human skeletal muscle stem cells (SkMCs) are isolated from the MI patients. Autologous transplantation of SkMCs into the infarcted heart has the advantages in cell isolation, in vitro culture, high survival rate under hypoxic conditions^[24], the unipotent to differentiate into contractile cells, without immune rejection, and no moral dilemma. Transplantation of SkMCs in human and animal models of MI suggests that the beneficial effect of this cell therapy is reducing left ventricle dilation by altering the expression profile of cardiac genes associated with left ventricle remodeling^[25,26]. Currently, the biggest obstacle regarding the use of SkMCs in clinical treatment is that the differentiated SkMCs do not express gap junction proteins, which can potentially induce arrhythmias in

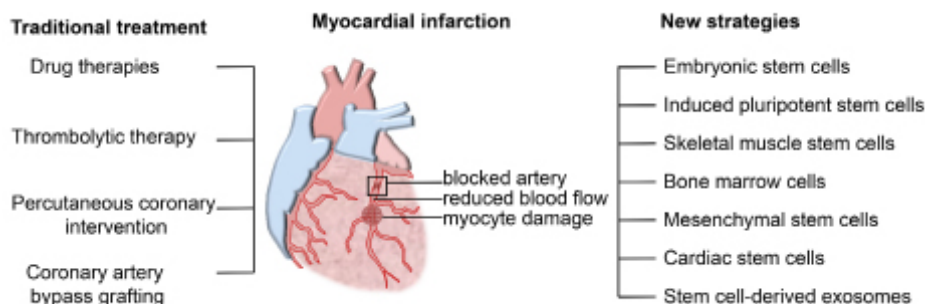


Figure 1 Traditional and new treatments for myocardial infarction.

recipient^[27]. However, this consequence was not proven in the first randomized placebo-controlled study and long-term follow up of the MI patients after skeletal myoblast transplantation^[13,28]. Further large animal model studies and clinical trials of SkMCs therapy may pay more attention to the effect of this therapy on the physiological function of the heart receiving the cells.

Bone marrow cells

Bone marrow cells (BMCs) are a kind of cells with the ability of self-renewal, proliferation, and differentiation. BMCs have the potential for multi-directional differentiation and are easy to dissociate^[29]. It can differentiate into cardiomyocytes in the cardiac microenvironment. In recent years, autologous bone marrow stem cell transplantation has become a hotspot in biomedical research because it circumvents the problem of immune rejection and bears no ethical concerns^[30,31]. For patients with myocardial infarction, bone marrow stem cell transplantation can significantly reduce myocardial infarction size, repair necrotic myocardium, and prevent ventricular remodeling, promote angiogenesis, and ultimately improve cardiac function^[32]. Clinical follow-up of Bone marrow transfer to enhance ST-elevation infarct regeneration (BOOST) trial indicated that intracoronary autologous BMC transfer leads to a mid-term improvement in echocardiographic parameters of diastolic function in patients after AMI^[33,34]. Currently, the study of the effect of intracoronary autologous BMC on left ventricular (LV) function within 24 h after successful reperfusion therapy demonstrates that intracoronary delivery of autologous BMC leads to an insignificant improvement in LV function at an early time point (< 24 h), but it demonstrates the safety and feasibility of clinically early intracoronary injection of BMC and suggests a vital role of BMC therapy in myocardial salvage and ventricular remodeling^[14]. BMC therapy treated AMI patients displayed a better quality of life (QoL) at 3 and 12 months post-AMI than the control-group patients^[35]. But the above findings stressed the need for long-term confirmation trials and for systematic assessment of cardiac function after BMC treatment.

Mesenchymal stem cells

Mesenchymal stem cells (MSCs) are a subset of non-hematopoietic adult stem cells that can be found in bone marrow, adipose tissue, amniotic fluid, liver, lung, spleen, placenta and umbilical cord blood^[36]. The multipotent MSCs are capable of differentiating into many cell types, including myocytes, osteoblasts, chondrocytes and adipocytes^[37]. MSCs can be easily isolated from the tissues of MI patients and expanded *in vitro*. Previous studies revealed that MSCs transplantation can prevent left ventricular remodeling and improve heart function without significant safety concerns^[38].

Though MSCs showed low cell retention and poor differentiation into cardiomyocytes, it still can enhance angiogenesis, inhibit cardiomyocytes apoptosis and fibrosis, and improve heart function^[12,39], suggesting that the transplanted MSCs modulate left ventricular remodeling after MI via a potential paracrine mechanism. The paracrine effects are attributed to the regulation of the NF- κ B signal pathway by Rap1, and selective inhibition of Rap1 in BM-MSCs showed reduced inflammation and enhanced cell survival that greatly improves heart function recovery following MI^[39]. Salvianolic acid B (Sal B) was reported to attenuate the apoptosis of MSC^[40], and transplantation of Sal B pretreated MSCs in rats improves cardiac function partly through the paracrine mechanism and promotes the differentiation of MSC toward endothelium cells^[41]. Hepatocyte growth factor (HGF), an important cytokine for angiogenesis, anti-inflammation and anti-apoptosis, was associated with enhanced angiogenesis, less cardiomyocyte apoptosis, increased proliferation of cardiomyocytes, and cardio-protective effects in a mouse MI model^[42]. However, currently the differentiation rate of transplanted bone marrow stem cells is relatively low, the fate of transplanted cells and whether MSCs will affect the function of other normal cells *in vivo* is not clear. As almost all studies and clinical trials were short-termed, long-term effects and the underlying mechanism of functional benefits remains to be uncovered to meet the clinical standard and government regulations.

Cardiac stem cells

With the continuous development of stem cell research, cardiac stem cells (CSCs) have been successfully isolated and identified. Cardiomyocyte stem cells are pluripotent stem cells in the heart and possess the potential to differentiate into various cardiac cells, including myocytes, smooth muscle and endothelial cells^[43]. In animal experiments, cardiac stem cells were injected into the heart of mice with heart disease, and the injected cells directly migrated to the damaged heart tissue, promoted the regeneration of myocardium, and improved the ability of the heart to pump blood^[44]. Multiple types of CSCs have been identified including Islet-1+ cells, Sca-1+ cells, cardiosphere derived cells (CDCs), cardiac mesoangioblasts, cardiac specific side population, and epicardial progenitors^[45-50]. A lot of preclinical researches in both small and large animal models have indicated the potential of CSCs therapy in treating MI (Table 1). Followed by the extensive study of CSCs in animal models, numerous clinical trials also paved the way for CSCs as new promising therapies that worth further exploring and application (Table 1).

Stem cell-derived exosomes

Recently, many stem cell types, including ESC, MSCs, and CSCs,

Table 1 Small/large animal model studies and clinical trails of CSCs therapy in treating MI.

Animal/Human	Cell Type	Outcomes	Ref.
Pig	CDCs	preserving ventricular function	[63]
Pig	CDCs	reducing IS and attenuating adverse acute remodeling	[64]
Pig	CDCs	decreasing scar, halting adverse remodeling, and increasing myocardial perfusion	[65]
Mouse	Isl1+	reduced infarct area, increased blood vessel formation and improved LV contractile function	[66]
Mouse	Bmi1+	contributing to the generation of de novo CM	[67]
Mouse	Sca1+	give rise to myocardial and vascular tissues, improve cardiac function	[68]
Mouse	Mesoangioblast	reducing postinfarction LV dysfunction	[69]
Human	CDCs	decreased scar size, increased viable myocardium, and improved myocardium function	[70]
Human	CDCs	augmented potency in ameliorating ventricular dysfunction	[71]

were found to secrete paracrine factors, such as exosomes and exosome-like vesicles^[51,52]. Given the high efficiency of exosomes to transport to donor cells, low toxicity, and high stability, it has been considered as a novel stem cell-derived strategies for MI treatment. ESC-derived exosomes from mouse were uncovered to stimulate neovascularization and restore heart function in mouse MI model. Moreover, ESC-derived exosomes were rich in miR-294 which can promote the survival and proliferation of CPCs^[53]. Exosomes secreted from mouse MSCs contained a lot of miR-22 that exerted an anti-apoptotic effect on cardiomyocytes, which restored heart function and reduced infarct size in mouse MI model^[54]. Exosomes isolated from human CPCs were rich in miR-210, miR-132, and miR-146a-3p, and injection of these exosomes significantly stimulated angiogenesis, suppressed apoptosis, and improved heart function in rat MI model^[55]. Therefore, these findings provide persuasive evidence that stem cell-derived exosomes exert beneficial effects on the treatment of MI in animal models. And it can be anticipated that stem cell-derived exosomes will soon be tested clinically as new strategies for heart regeneration therapy in MI treatment.

CONCLUSION

In summary, myocardial infarction mainly leads to myocardial ischemic necrosis that will result in death. At present, the treatment of myocardial infarction mainly includes drug therapy, thrombolytic therapy, and percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG) surgery. All these treatments can prevent ventricular remodeling, and to some extent, relieve the symptoms of myocardial ischemia, but all of them have some limitations.

In the stem-cell transplantation trials, researchers revealed that the transplanted stem cells, including bone marrow stem cells, inducible pluripotent stem cells, and cardiac stem cells, survived only for a few weeks in the animal model of ischemic heart disease^[56]. Various strategies have been tested to overcome the low survival rate of stem cells after transplantation in heart tissue, but due to different measurements were used in these studies, a unified standard that measuring the efficacies of approaches improving cell retention is required to determine the optimal strategy^[57]. In addition, human embryonic stem cell (hESC) and inducible functional stem cell (iPSC) lines showed increased frequency of specific gene aberrations, thus, it requires frequent genetic testing of pluripotent stem cells to ensure its stability and clinical safety^[58,59]. Therefore, although stem cell transplantation has a bright future, a cautious attitude needs to be maintained towards clinical trials of stem cell transplantation for the treatment of patients with myocardial infarction.

The adult human heart possess limited capacity to generate cardiomyocytes^[60]. Along with the growth of age, the regenerative rate of the cardiomyocyte is gradually slow down. At age 25 the

annually regenerative rate is approximately 1% and at age 75 the regenerative rate is reduced to 0.45%. Approximately half of the cardiomyocytes are renewed in human life expectancy^[60]. But if the human cardiomyocyte has the ability of regeneration, why most of the cardiomyocyte exit the cell cycle? How to use the potential regenerative ability of cardiomyocytes to restore the damaged cardiomyocyte? In clinical trials, the test and application of stem cell transplantation confront with various problems and are hindered by numerous restrictions. The regenerative ability of cardiomyocytes will undoubtedly provide new research direction to the researchers. Coincidentally, it has been found that Akt1 dramatically enhances and expedites the formation of induced cardiac-like myocytes from fibroblasts in the presence of cardiac transcription factors GATA4, Mef2c, Hand2, and Tbx5^[61]. In addition, the cardiac side population, the first population of cardiac progenitor cells identified in the adult heart, can differentiate into cardiac lineages in response to cardiac injury, and thus could be a promising target for cardiac regenerative medicine^[62]. The research concerning the usage of the regenerative ability of cardiomyocytes for heart regeneration has just started, but many exciting findings have been reported in just a few years. In the near future, these results will be applied to human studies and clinical treatments and bring the gospel to patients with myocardial infarction.

Myocardial regeneration strategy can not only prevent ventricular remodeling, but also repair the necrotic myocardium and provide a fundamental cure for patients with myocardial infarction. But the study of myocardial regeneration has just started. We believe that with the deepening study and discovery of myocardial regeneration, it will become a powerful clinical tool for the treatment of myocardial infarction in the near future.

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