

Cell-based therapy for myocardial regeneration



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ABSTRACT

Myocardial infarction is one of the main cause of mortality in many countries. Therefore, an effective therapy for myocardial infarction is required. Reperfusion and other conventional therapy have been the mainstay therapy for myocardial infarction. However, many patients remain refractory to this therapy. Cell-based therapy is considered a novel therapy, in which stem cells are used for cardiac repair. Stem cells are potential therapeutic and promising option that could be the alternative solution for salvaging damaged cardiomyocyte.

Based on current studies, stem cells are a promising therapeutic approach for myocardial infarction. However, some challenges need to be answered by future studies before this novel therapy can be widely applied. This essay provides an overview of the progress in stem cell therapy for myocardial infarction.

INTRODUCTION

The robust potential of stem cells were still a mystery, but today, we are constantly getting new information on this particular topic. One of the prospects of stem cell therapy is to treat damaged cardiomyocyte (Fischer, et. al, 2009; Beltrami, 2003). Acute myocardial infarction is one of the main causes of mortality and morbidity in many countries. Not only this disease causes a massive socio-economic burden, but also reduces the quality of live for patients who survive the attack (Hamm, 2016). Currently, one of the mainstay therapy for myocardial infarction is rapid revascularization to limit ischaemic damage. Reperfusion and other conventional therapy have undoubtedly saved so many lives, yet there are patients remained refractory

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to this therapy and left with no other treatment options. In addition to that, many patients who have underwent reperfusion strategy and survived, often left with significant impairment of left ventricular systolic function. One big question remain unanswered. Is there any other treatment option for these patients? Medical therapeutic approach to reduce damaged cardiomyocyte and generate new functioning muscle is the current unmeet need.

Stem cells emerge as the novel procedure to restore damaged cardiomyocytes, and this procedure is popularly known as cellular cardiomyoplasty (Pendyala, et. al, 2008; Reinlib, 2000). Many preclinical and clinical trials have documented the potential use of stem cells to generate viable cardiomyocyte and improve cardiac function (Bergmann, et. al, 2009). To date, there are many different types of adult stem cells and progenitor cells used for this procedure, some of which are bone marrow derived stem cells, hematopoietic stem cells, mesenchymal stem cells and so on. Since the advance of stem cells technology is faster than ever before, this essay aimed to give an evidence based update on stem cells use for myocardial infarction, what we have achieved so far, and what does the future hold for this breakthrough.

CELL-BASED THERAPY FOR MYOCARDIAL REGENERATION

After an ischaemic attack due to occluded coronary vessels, heart muscle usually left damaged and nonfunctioning. However, recent evidence suggested that the cardiac muscle could actually undergo a limited amount of renewal. A prospect of inducing muscle cell to undergo division for

cardiomyocyte replacement, or generating new muscle by stem cells are certainly intriguing (Roell, et. al, 2002; Santoso, et. al, 2011).

Stem cells are capable to proliferate in the same state (self-renewal) and differentiate into multiple cell lineages. On the other hand, progenitor cells are more specific and have limited differentiation potential. Mechanism on how stem cells work are as follows: firstly, these stem cells need to be extracted from the source (eg. bone marrow), after that these stem cells need to be delivered to the injured area. These cells are implanted in the myocardium, and due to the nature of these cells, they would grow and differentiate/transdifferentiate into cardiomyocyte. To achieve the goal of cardiac repair, these cells should also have the ability to fuse with the surrounding tissues that their harmonious contraction increases the heart contraction. Furthermore, these newly-formed cardiomyocyte should also express the appropriate electromechanical properties required for contraction to yield a synchronous contraction (Templin, et. al, 2011; Makino, et. al, 1999).

Many clinical studies have documented the feasibility and safety of cellular cardiomyoplasty in patients with coronary artery disease (Makino, et. al, 1999; Strauer, et. al, 2002). To date, there are some different types of adult stem cells and progenitor cells used for this procedure, some of which are bone marrow derived stem cells, hematopoietic stem cells, mesenchymal stem cells and many others (Jackson, et. al, et. al, 2001; Kamihata, et. al, 2001; Bolli, et. al, 2011)

POTENTIAL SOURCE AND TYPE OF STEM CELLS

Bone Marrow Derived Stem Cells

Bone marrow derived stem cells (BMCs) are the most widely studied type of stem cells. Orlic et al. (2001) first describe the ability of bone marrow cells to regenerate infarcted myocardium in mouse models. The transplanted cells showed transdifferentiation into cardiomyocyte which eventually lead to improved left ventricular ejection fraction (Orlic, 2001). The three types of stem cells derived from bone marrow are hematopoietic stem cells (HSCs), mesenchymal stem cells (MSCs), and endothelial progenitor cells (EPCs) (Orlic, 2001; Piao, et. al, 2005; Badorff, et. al, 2003).

The role of BMCs for acute myocardial infarction has been reported to improve left ventricular ejection fraction (LVEF), both in REPAIR-AMI and BOOST trial (Meyer, et. al, 2006; Schachinger, et. al, 2006). BOOST trial demonstrate an acceleration of LVEF after intracoronary BMCs transfer (ejection fraction increased by 6.7% in the BMCs group as compared to 0.7% in the control group), and significant result was sustained until 18 months (Meyer, et. al, 2006). While in REPAIR AMI trial, improvement of LVEF, infarct size and wall thickening of infarcted segments were reported at two years follow up. At two years, the cumulative end point of death, myocardial infarction, or necessity for revascularization was significantly reduced in the BMC group compared with placebo (hazard ratio, 0.58; 95% CI, 0.36 to 0.94; P= 0.025) (Assmus, et. al, 2010; Perin, et. al, 2012).

Skeletal Myoblast

Skeletal muscle has the ability to regenerate under certain circumstances. Skeletal resident stem cells are usually known as satellite cells, and these cells would differentiate to new myocytes in response to injury. However, whether this ability can be translated to a different condition, as in cardiomyocyte repair, should be further studied (Taylor, 198; Reinecke, et. al, 2002). MAGIC trial, a randomized controlled phase II trial, showed no significant changes in terms of global and regional LV function in skeletal myoblast- treated patients (Mensche, et. al, 2008). Another study performed by Dib et al.(2005) showed an increased in LV ejection fraction in the group treated with transepical injection of autologous SMs.

Mesenchymal Stem Cells

Mesenchymal stem cells (MSCs) are another potential option for cellular cardiomyoplasty. Mesenchymal stem cells can be found in various tissue, such as bone marrow and adipose tissue (Pittenger, 2004). One interesting mechanism by which MSCs mediate cardiac function improvement is the paracrine effect. MSCs may secrete soluble cytokines and growth factors that would eventually influence adjacent cardiomyocyte (Gharaibeh, et. al, 2011).

Hare JM et al. (2009) studied the efficacy of intravenous allogenic human mesenchymal stem cells in patients with myocardial infarction. According to this study, intravenous MSCs were safe as showed by the similar adverse event rates in both intervention and control group. MSCs injection favorably affected patient functional capacity, quality of life and LV remodeling (Hare, et. al, 2012).

Endothelial Progenitor Cells

Endothelial progenitor cells (EPCs) have been linked with neovascularization in ischemic tissue. This interesting finding lead to the use of EPCs for another therapeutic purpose like cellular cardiomyoplasty (Isner, et. al, 1999). The human peripheral blood-derived EPCs would be a potential approach because those cells can be easily isolated without the need of major surgical intervention (Lin, et. Al, 2000).

This assumption was later confirmed by Badorff et al. In this study, Badorff et al. (2003) reported that EPCs from healthy volunteers and Coronary Artery Disease (CAD) patients can transdifferentiate into functionally active cardiomyocytes when co-cultivated with rat cardiomyocytes. However, this finding was later opposed by Gruh I et al. According to this study, there was no significant evidence of transdifferentiation of human EPCs into cardiomyocyte (Gruh, et. al, 2006).

Resident Cardiac Stem Cells

Until recently, we believe that heart is a fully mature organ with no capability of self-renewal. However, the adult heart is not a terminally differentiated organ, but harbors stem cell with regenerative capacity, namely resident cardiac stem cells (CSCs). Although the origins of CSCs are yet unclear, they can be isolated from heart tissue and expanded ex vivo for use as a cell-based therapy. There were many types of CSCs have been described in previous studies, like: epicardium-derived cells, cardiosphere-derived cardiac cells, and cardiac Sca-1+ cells. These resident stem cells have the potential

to differentiate into different types of cells like vascular smooth muscle and myocardial cells (Tang, et. al, 2013; Tang, et. al, 2006; Fazel, et. al, 2006).

Embryonic Stem Cells and Induced Pluripotent Stem Cells (iPS)

Embryonic stem cells (ESC) are derived from the blastocyst (inner cell mass) of human embryo prior to implantation. ESCs are pluripotent cells, which means they have the capability to differentiate into any cells, one of which is cardiac myocytes. Due to the source of these cells, there are ethical issues regarding the use of ESC (Kofidis, 2005). The huge potential of ESC comes with a price. The pluripotency of ESC made these cells predisposes to tumor formation including teratomas. Amariglio N et al. (2009) documented the occurrence of a human brain tumour following neural stem cell therapy. A boy with telangiectasia was treated with intracerebellar and intrathecal injection of human fetal neural stem cells. Four years later, he was diagnosed with a multifocal brain tumour. After thorough analysis, the tumor was of nonhost origin, indicating it was derived from the transplanted neural stem cells (Amariglio, 2009). To date, due to the scarcity of studies on ESC and negative experiences of previous studies, the significance of ESC as cell-based therapy for myocardial infarction remains elusive. The above-mentioned limitation would hopefully be elucidated in future research.

Human Umbilical Cord Blood Cells

Human umbilical cord blood cells (hUCB) contains a large number of non-hematopoietic stem cells which rarely express human leukocyte antigen (HLA) class II antigens, thus reducing the risk of rejection. Many studies have reported the efficacy and safety of hUCB administration in acute myocardial

infarction model, with conflicting result (Henning, 2004; Moelker, 2007).

According to Henning RJ et al. (2004) hUCB administration reduce infarction size and improve ventricular function in rats without requirements for immunosuppression (Henning, 2004). Similar positive finding were documented by Kim et al.

Circulating Blood-derived Progenitor cells

Circulating blood-derived progenitor cells (CPCs) are similar to BMCs, which mainly composed of EPCs. Santoso T et al. (2011) studied the safety and feasibility of combined granulocyte colony stimulating factor (G-CSF) and erythropoietin (EPO) based-stem cell therapy using intracoronary infusion of peripheral blood stem cells in patients with recent anterior myocardial infarction. G-CSF is used to mobilized stem cells to the injured area, inhibits cardiomyocyte apoptosis, promotes neovascularization, and increase the production of nitric oxide. While EPO, that is originally thought to be a hematopoietic hormone only, also may inhibited apoptosis and induced angiogenesis. This phase I study concluded that this procedure is safe and resulted in improved endpoints for LV ejection fraction and cardiac viability (Santoso, 2011).

Cardiopoietic Stem Cells

Cardiopoietic stem cells are not a distinct type of stem cells but refer to the novel way of processing stem cells in order to get a lineage specification. Cardiopoietic stem cells are harvested stem cells that are treated with a protein cocktail to replicate natural cues to heart development, before being injected into the patient's heart. The C-CURE trial studied the efficacy of

bone marrow derived-mesenchymal stem cells in chronic heart failure. The isolated mesenchymal stem cells were exposed to a cardiogenic cocktail that trigger expression and nuclear translocation of cardiac transcription factors, before being injected to the patient's heart. After six months follow up, patients in the treatment group significantly improved in terms of LVEF and fitness capacity. There was no evidence of increased cardiac or systemic toxicity induced by cardiopoietic cell therapy (Bartunek, 2013).

Unfortunately, data comparing the efficacy and safety between cardiopoietic stem cells and ordinary stem cells without cocktail-based priming is still lacking.

DELIVERY METHODS

In order to make these stem cells reach the heart, a reliable delivery method need to be employed. The ideal method should be able to safely and efficiently deliver an optimal number of stem cells to the target tissue. Beside the high efficacy, this delivery method should be as minimally invasive as possible for the sake of patients' comfort. There are some delivery methods worthy to know.

Intracoronary Infusion

As the name implies, intracoronary infusion is a process of delivering stem cells through coronary artery, usually through intracoronary catheterization. Stem cells are infused under pressure via a ballon catheter. The ballon was inflated in order to prevent anterogade blood flow that would compromise stem cells delivery. Catheter guided cell transfer has its unique advantage of safety under local anesthesia, and a part of routine cardiac catheterization. The intracoronary method provide a maximum number of cells to the target

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area, with good blood supply which is crucial for cell survival. Multiple studies have reported the use of intracoronary infusion for stem cells delivery (Strauer, 2002; Schachinger, 2006).

Intravenous Peripheral Infusion

Intravenous stem cells administration is one of the easiest method to be employed. Intravenous administration is possible through homing phenomenon of stem cells to the injured heart. Unfortunately, intravenous peripheral infusion comes with some disadvantages. First, only 3% of normal cardiac output will flow per minute through the left ventricle. This low amount of blood would limit the amount of stem cells delivered. Secondly, due to the passing of venous blood in the lung, many cells would trap in lung vasculature that eventually lead to stem cells reduction (Grieve et. al, 2012).

Intramyocardial, Transendocardial and Transpericardial Route

As mentioned earlier, the downside of intravenous administration is the passing of the blood in certain organs that would entrapped some of the stem cells. Unlike intravenous route, intramyocardial method is undoubtedly provide direct access to the injured cardiomyocyte bypassing the need for mobilization, homing and any risk of cells entrapment in other organ, thus provide a more effective way to deliver abundant stem cells to the injured area. However, this method comes with its own expense of a more invasive method, not to mention the risk of ventricular perforation in the already damaged cardiomyocyte. Intramyocardial delivery usually performed during an open heart surgery or needle-tipped delivery catheter (Strauer, 2003; Forrester, 2003). Nelson et al.(2009) documented that intramyocardial

delivery of iPS originating from reprogrammed fibroblast, yielded progeny that properly engrafted and resulted in restored contractile performance, increased ventricular wall thickness, and electric stability (Nelson, et. al, 2009).

STUDIES USING STEM CELLS IN MYOCARDIAL INFARCTION

Many studies have been carried out to investigate the efficacy and safety of stem cell therapy in patients with myocardial infarction. Each of these studies investigated different kind of stem cells with different delivery methods. The ultimate goal of these studies is to answer whether stem cell therapy could be a feasible therapeutic approach for patients with myocardial infarction. The result of these studies were not always positive, even some of the studies did not document any beneficial effect of stem cell therapy. However, this conflicting result need to be intepreted with caution due to the different study method, different type of stem cells used, and different delivery methods employed.

Three meta- analysis on the efficacy of BMCs therapy for myocardial infarction have been published. In a meta-analysis by Delewi R et al, intracoronary BMCs infusion is associated with improvement of LV function and remodelling in patients after ST-segment elevation myocardial infarction. The benefit in terms of LVEF improvement was more pronounced in patients with a worse baseline LVEF (LVEF cut off: 40%) and younger age (age cut off: 55 years) (Delewi, et. al, 2013). In a second meta-analysis by Clifford DM et al. (2012) which include thirty-three RCTs, there was no significant difference in hard end point like mortality and morbidity in the BMCs treated group. However global heart function, as represented by LVEF

and infarct size, was improved significantly and was sustained long term (12 to 61 months) in the BMCs group (Clifford, et. al, 2012). The third meta-analysis by Long C et al. (2013) further confirmed the beneficial effect of intracoronary BMCs in patients with acute myocardial infraction. According to this meta-analysis, BMCs therapy significantly improved LVEF, while mildly but not significantly reduced left ventricular end-systolic volume and left ventricular end-diastolic volume (Lond, et. al, 2013). These three meta-analysis synonymously agree that BMCs therapy is beneficial in terms of improved heart function and reduced infarct size.

CHALLENGES AND THE FUTURE

We have just entered the new era of stem cell therapy. When advanced therapy like primary PCI and thrombolytic showed more limited beneficial for patients with myocardial infarction, the concept of cell-based therapy is definitely appealing. This new approach could be the answer that have been waited for sometime.

As we have discussed previously, there are many issues on stem cell therapy that need to be addressed in future studies. Firstly, what is considered to be the best stem cells to replace cardiomyocyte. Secondly, the right delivery method of these stem cells need to be determined. Whether different type of stem cells required certain delivery methods also need to be further elucidated. Another question is the right timing of delivery (acute, sub-acute or chronic), whether it contributes to the fate of stem cells. Fourth, the concentration of stem cells, dose-effect relationship and safety of stem cell therapy need to be further investigated. One particular topic in regard to stem cell safety is the tumorigenicity of ESC. We need to disentangle a way

to reprogram these cells so they can differentiate into functional cells, but lack the ability to form tumours. Finally, novel diagnostic tools are required to detect and evaluate stem cells therapy. Future studies would hopefully provide solid proof on hard end-points (eg. mortality), instead of surrogate markers like LVEF or infarct size.

CONCLUSION

Tremendous progresses were made in cell-based therapy, and future advances would further lead us to a new solution for ischaemic heart disease. Stem cells own robust potential in medicine, one of which is to replace damaged cardiomyocyte. More evidents are needed in advance to widely use of this modality.

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