Stem Cells for Use in Regenerative Medicine Post Myocardial Infarction

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Abstract

Myocardial infarction is a condition that has degenerative effects on the heart, even after being stopped by initial treatment. Under normal circumstances, a large infarcted area is left behind, which results in gradual degradation of the heart until total shutdown occurs. As such, it is necessary to find a therapy that can provide regenerative properties to the infarcted region. Stem cell therapy, particularly Induced Pluripotent Stem Cells (iPSCs) and Mesenchymal Stem Cells (MSCs) are a possible source of treatment for Myocardial Infarctions. MSCs induce neovascularization within the infarcted regions via angiogenic and antiapoptotic factors and halts cardiac degeneration. iPSCs can differentiate into cardiomyocytes and have been proven to regenerate mechanical contractility in infarcted regions of the heart.

Background

Myocardial Infarction is a dangerous heart condition in which blood flow to the coronary artery is either slowed or halted entirely. Such a condition results in low or even no oxygen supply to the heart, which can cause a range of severity depending on the size of the blockage and amount of blood flow.[1] Regardless of severity, a cardiac infarction usually results in some amount of cell death of cardiac and vascular tissue in the heart, which the body subsequently partially repairs through the formation of scar tissue.[2] Despite this repair, scar tissue does not operate to the same efficiency as the original cardiac tissue, as it acts akin to a placeholder of the dead tissue to prevent necrosis of surrounding area rather than functional tissue that assists in function of the heart. Accumulation of scar tissue over the long-term presents a detriment to the individual, as they run the risk for afflictions such as arrythmia, aneurysm, or inflammation of the heart. Considering the long-term complication associated with myocardial infarctions, there is a need for some type of regenerative medicine which can reverse the scarring process and reintroduce proliferation of original cardiac tissue onto the scar site.

Developments in Stem Cell therapy have given rise to a multitude of potential remedies to post-myocardial infarction complications, such as Mesenchymal Stem Cells (MSCs) and induced pluripotent stem cells (iPSCs), which will be the primary focuses of this paper. Each of these stem cell types provide a significant reduction in scar tissue and provide regenerative properties to areas of the heart afflicted by an infarction.

Human iPSCs have exciting potential for treatments because of their ability to avoid immune rejection and they have the same properties as Embryonic stem cells (ESCs) without social and ethical issues [3] associated with sourcing ESCs. IPSCs can be sourced from any somatic cells in the body, and their autologous behavior prevents the occurrence of a significant immune response to sheeted or injected iPSCs into infarcted regions of the heart.

MSCs injected into subjects post myocardial infarction have been found to participate in vasculogenisis and angiogenesis via paracrine signaling and integrate these new blood vessels into native host tissue.[4] These subjects, when observed over a span of 8 weeks (about 2 months), were found to have an increase in tissue perfusion, a decrease in infarction size, as well as a lower degree of apoptosis of cardiomyocytes when compared to control subjects which underwent induced Myocardial Infarction without the administration of MSC's at all.

Main Body:

Consequences of a myocardial Infarction

A Myocardial infarction (MI) results in lasting damages to the heart muscle which can cause permanent problems in the diastolic and systolic function. MI can lead patients to different complications like arrhythmic, mechanical, and inflammatory sequelae. In real life the above can be translated to low physical health and activity which is related and negatively affects the return of the patient to work.[5] One of the most serious is cardiogenic shock. It affects around 7% of patients who suffer from myocardial infarction and its responsible for most of the deaths related to MI. The left ventricular myocardium is usually the one that gets damaged.[6]

Treatment methods using stem cells (Stem cell based therapies)

Current therapeutic advances and strategies in MI treatment are limited to thrombus removal, blood perfusion and heart transplantation,[7] but these methods cannot restore the dead myocardial cells and sometimes are difficult to apply because of the lack of donors and the high risk associated with the surgeries. Therefore, the most valuable and promising treatment methods involve stem cell therapies such as: inducing stem cells into becoming cardiac cells after injection into the patient, and growing tissue in vitro that will replace dead cells by being grafted the damaged areas. For the first method, the autologous stem cells are isolated from the patients and get expanded according to specific culture protocols to get the amount and purity that is being needed for the therapy. Then stem cells are activated, followed by an induction of cardiomyocyte differentiation before getting injected to the injured heart. The second method is used worldwide in different laboratories and clinics by specialists that grow cardiac tissue with the help of stem cells and synthetic scaffolds. There are 3 strategies by which scientists can grow and engineer heart tissue in vitro: cardiac myocytes seeding on synthetic matrices; entrapment of cardiomyocytes in collagen by combining stem cells, soluble collagen, and ECM; and the last one is by putting together monolayers to make a multilayer construct.[8] Cell types currently used for therapeutic purposes include pluripotent stem cells such as embryonic stem cells and induced pluripotent stem cells, and adult stem cells such as mesenchymal cells, epithelial stem cells, and somatic cells.[9] In this paper we will discuss the potential of induced pluripotent stem cells and mesenchymal stem cells for treatment of MIs.

Induced pluripotent stem cells (iPSCs)

Induced pluripotent stem cells (iPSCs) are pluripotent stem cells that have been produced from adult somatic cells and must go through a genetic reprogramming process. Embryonic stem cells and iPSCs have similar properties like self-renewal and the ability to change into different types of cells in the body.[10] Human Induced pluripotent stem cells offer an extraordinary prospect to think about human physiology and illness at the cellular level. This articulation expansively alludes to the origin of iPSC lines, their utilization for cardiovascular disease modeling, their utilization for accurate medication, and approaches through which to fortify their more extensive utilization for biomedical employment.[11] There are potential challenges and benefits to the use of induced pluripotent stem cells. These stem cells do not provoke severe immune rejection by heart tissue.[12] Different research has shown that pluripotent stem cells delivered by cardiomyocytes have a significant effect on myocardial infarction, by restoring the mechanical contractility after transplantation into the destroyed area.[13-15]

Research has shown how human iPSC-CMs can improve myocardial function after myocardial infarction[15]. In this paper they used rats that received the iPSCs, which were reprogrammed under a GMP grade lab, and the cardiac function was analyzed by echocardiography. With the use of the fluorescent cell tracer Vibrant, the researchers were able to detect the grafted cardiomyocytes to check the survival of the cells. As seen in Fig. 1 (a, b, c) one month after ligation, the control group of rats that were treated only with 5% of albumin solution for infarcted hearts had a significantly decreased left ventricular ejection fraction and decreased fractional shortenings. The rats that were injected with iPSC-CMs seemed to improve the ejection fraction and the fraction shortening. In addition, the left ventricular wall was significantly thicker in the rats under iPSC-CMs in contrast to the control group (Fig.1a, h). From these findings, they, reported the improvement of myocardial function after MI with the use of iPSC-CMs.

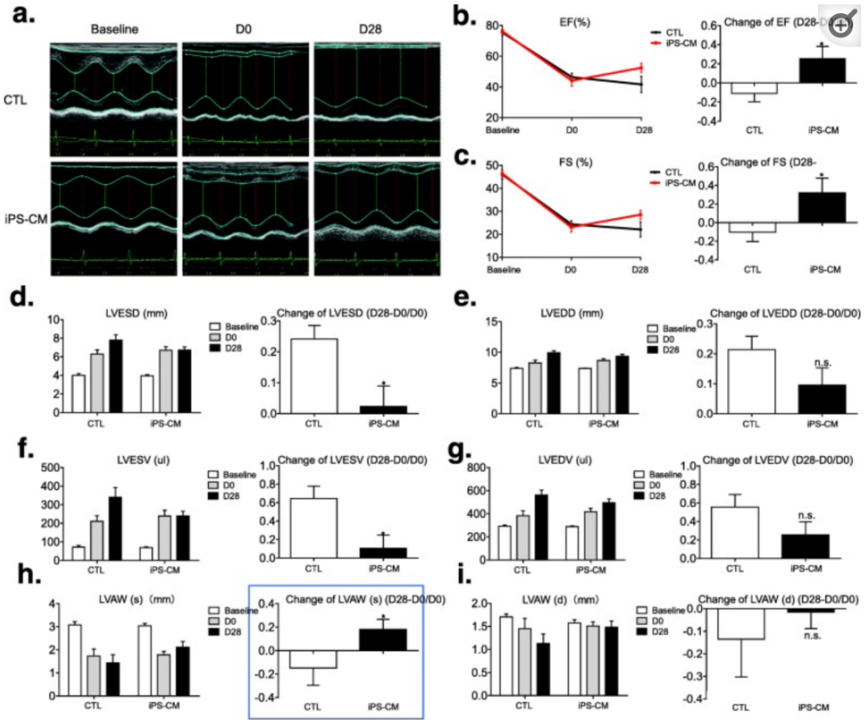

Figure 1. [a] *Left ventricular function following human iPSC-CM therapy. a Representative images of hearts at baseline (before MI model established), D0 (10 days after LAD coronary artery ligation and before iPSC-CM grafting) and D28 (4 weeks after iPSC-CM grafting) with administration of 5% albumin solution (CTL group) (upper) versus iPSC-CMs (iPS-CM group) (lower). b Quantification of left ventricular ejection fraction (EF) and change of EF (D28-D0/D0) demonstrated a trend toward improved functional recovery at 4 weeks after the second thoracotomy in the iPS-CM group compared with the CTL group. c Quantification of left ventricular fractional shortening (FS) and change of FS (D28-D0/D0) demonstrated a trend toward improved functional recovery at 4 weeks after the second thoracotomy in the iPS-CM group compared with the CTL group. d–iQuantification of left ventricular end-systolic diameter (LVESD), left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic volume (LVESV), left ventricular end-diastolic volume (LVEDV), end-systolic and end-diastolic left ventricular anterior wall (LVAW) thickness and changes in these indicators. iPSC-CMs induced pluripotent stem cell-derived cardiomyocytes, MI myocardial infarction, LAD left anterior descending, CTL control, LVAW(s) left ventricular anterior wall thickness (end-systolic), LVAW(d) left ventricular anterior wall thickness (end-diastolic). (CTL group: n = 8; iPS-CM group: n = 9). Unpaired two-tailed t-test with * vs CTL $P < 0.05$, n.s. = not significant*

[a] *Diagrams sourced from Guan et al. (2020)*

Other researchers[16] have analyzed the heart and with the use of iPSCs to repair myocardial infarction. Two weeks after performing LAD ligation and induce the mice with iPSCs, iPSC-CM purity was higher 99%. The iPSC-CMs built mature grafts in the myocardium and improved significantly the left ventricular function. So, the research team conclude that iPSC therapy is a very useful tool against MI and can be used for improvements of the myocardial function.

Mesenchymal Stem Cells (MSCs)

Mesenchymal Stem Cells (MSCs) are a type of adult stem cell which is derived from either the bone marrow or adipose tissue microenvironments but follow a similar affinity for differentiation into several cell lineages regardless of origin. Under normal circumstances, a major myocardial infarction results in a high degree of tissue necrotizing due to the reduced oxygen supply because of arterial blockage to the point where the heart can no longer operate efficiently and will slowly degenerate until total organ failure occurs.[1] Research as to the efficacy of MSC transplantation on infarcted regions of the heart has been done, and results show promise when it comes to halting the degeneration process as well as some degree of differentiation and proliferation of MSCs into cardiomyocytes, endothelial, and smooth muscle cell lines.

Specifically, research[4] was conducted to probe the effects on the infarcted regions when a monolayer of MSCs were transplanted onto the infarction. Before being transplanted, however, the monolayer was stained with GFP to fluoresce as to keep track of the cells as they spread as well as track any differentiation which may have occurred on the monolayer. From this research, it was found that there were a high amount of angiogenesis (VEGF-Vascular Endothelial Growth Factor) and antiapoptotic factors (HGF-Hepatocyte Growth Factor) which were expressed, indicating a level of paracrine response triggered by the presence of the MSC monolayer, allowing for a measure of repair in the infarcted region, which cascaded into a halting of cardiac degeneration and increased survival rate in test subjects in which infarctions were induced and were then administer MSCs.

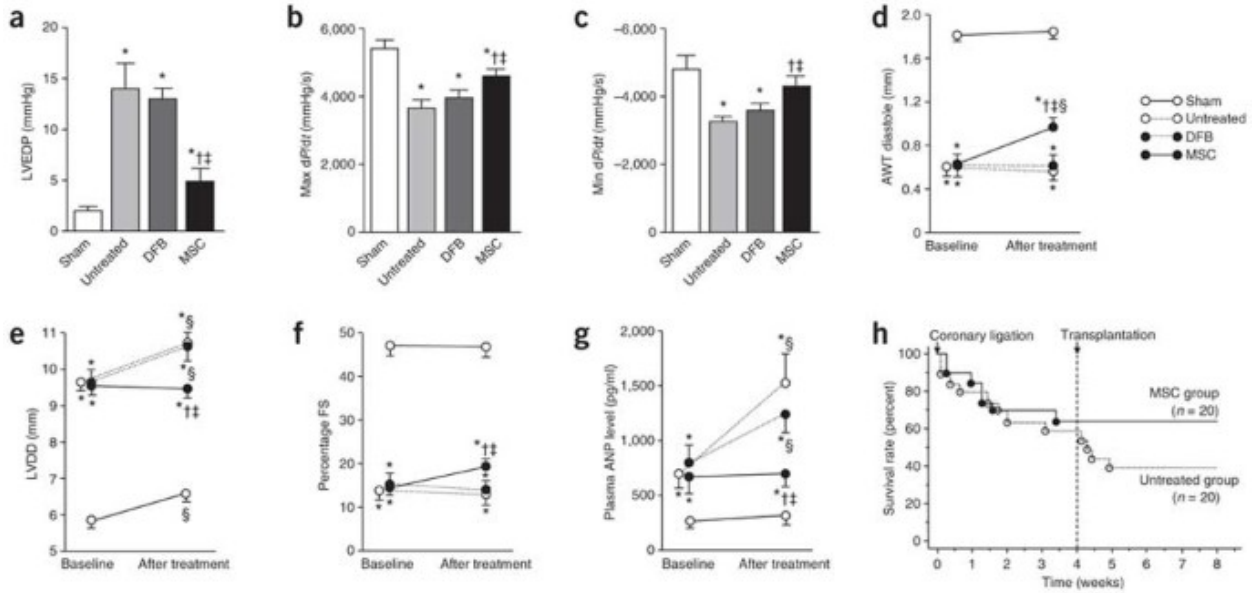

Figure 2: [b] *(a–c) Hemodynamic parameters obtained by catheterization. LVEDP, left ventricle end-diastolic pressure. (d–f) Echocardiographic findings. AWT, anterior wall thickness; LVDD, left ventricle end-diastolic dimension; FS, fractional shortening. (g) Plasma a trial natriuretic peptide (ANP) level. Baseline represents measurements 4 weeks after coronary ligation; 'after treatment' represents measurements taken 4 weeks after transplantation (8 weeks after coronary ligation). Data are mean ± s.e.m.* $^{*}P < 0.05$ *versus sham group;* $^{\dagger}P < 0.05$ *versus untreated group;* $^{\ddagger}P < 0.05$ *versus DFB group;* $^{\S}P < 0.05$ *versus baseline. (**h**) Survival of rats with chronic heart failure with or without monolayered MSC transplantation. The Kaplan-Meier*

survival curve demonstrates an 8-week survival rate of 65% for the MSC group versus 45% for the untreated group. Survival rate after transplantation was significantly higher in the MSC group than in the untreated group (100% versus 71% 4-week survival rate after transplantation, log-rank test, P *< 0.05).*
[b] *Diagrams sourced from Miyahara et al. (2006)*

This repair of infarcted regions is evident, as Left Ventricle End-Diastolic Pressure (LVEDP) seemed to normalize near the levels of a healthy heart (Notated as "Sham" in this model) 4 weeks post treatment, as well as the dPdt of the LVEDP being similar to that of a healthy heart when compared to rat subjects that received a placebo transplantation as well as untreated rats. From this data, and especially Fig. 2.h., there is an evident link between the implantation of the MSC's and a regenerative effect on infarcted regions of the myocardium, as well as a halting in the normal degeneration process which occurs in subjects that do not have their myocardial infarctions treated.

There is a limitation to this regeneration, however. Within the same study, the researchers tried to test for a measure of differentiation within the MSC monolayer that was implanted onto the infarcted region of test rats, however the results demonstrated the effect of the MSCs were mainly of a paracrine nature, allowing for neovascularization through differentiation into minor vascular networks within the infarcted region, and some differentiation into cardiomyocytes, evident through staining for specific markers indicating the presence of such cell lines, but the vast majority of the cells within the monolayer exhibited signs of undifferentiated MSCs. Although the growth of the monolayer sustained enough pressure to allow left ventricle attenuation post-infarction, very little was done in the way of differentiation to allow for any real regeneration of the infarcted region to occur. Additionally, research[17] has shown that although autologous MSCs are considered immunoprivileged and do not invoke an immune response, allogenic MSCs cannot be utilized, which prevents any sourcing beyond the patient who have MSCs administered as a solution to myocardial infarction.

Conclusions

To summarize, the utilization of stem cells in regenerative medicine when it pertains to treatment post-myocardial infarction is an exciting development which has some merit in the stabilization of the heart post-infarction, especially regarding iPSC and MSC cell lines. Induced pluripotent stem cells can be differentiated into cardiomyocytes and can viably be differentiated into cardiomyocytes and be genetically enhanced to high purity. Human iPSC-CMs transplantation can improve the myocardial function and can reduce the mortality in rats under myocardial infarction. Also, the grafted cardiomyocytes have been proven to be able to be detected even after 1 month after the transplantation which helps for the promotion of the myocardial regeneration.

MSCs have been proven to proliferate when transplanted onto infarcted regions of the heart, which has proven to attenuate the left ventricle, which is usually damaged and has some area of it necrotized due to hypoxia during a myocardial infarction. Additionally, MSCs have been proven to induce neovascularization through angiogenic and antiapoptotic factors, stabilizing the degradation of the myocardium which would usually occur after an infarction. The downside to the use of MSCs is the low rate of differentiation into integral cardiac tissue such as cardiomyocytes, as well as the need for purely autologous MSCs to prevent an immune response, which prevents the creation of pre-prevention MSC transplantation or injections post infarction and requires a specifically tailored MSC line to be manufactured for treatment.

The current stem cell therapies described have promise when it comes to the treatment of myocardia infarctions, however there are limitations to each therapy. Finding a way to modify the MSCs to differentiate more readily into cardiomyocytes and other tissues originally present in the infarcted area would be beneficial, as differentiation would allow for actual regeneration of the infarcted area instead of merely stabilizing the region from further degeneration. Additionally, finding a way to reach maturity in iPSCs that is akin to adult cardiomyocytes rather than the current fetal cardiomyocytes they differentiate into would yield better results in terms of integration into native tissue and regeneration of the infarcted area.

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