



Review Article

Mesenchymal Stem Cells and Cardiovascular Diseases

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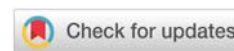
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Abstract

Stem cell therapy has begun as a promising and novel approach for the treatment of various diseases. Stem cell therapy involves the identification of correct cells, area of transplantation. Transplantation of functional and healthy stem cells help to renewal of damaged cells and repair injured tissue. Stem cell isolated from bone marrow were the first cell type used in preclinical and clinical investigations for the have been extended to the use of various populations of stem cells. But there are very few studies which show the roles of stem cells in cardiovascular disease. Cardiovascular Disease (CVD) constitutes the most important cause of mortality and morbidity worldwide. CVD represents a group of disorders connected with the defeat of cardiac function. In spite of significant advances in the understanding of the pathophysiological mechanisms of the disease, the problem of cardiac tissue loss has not yet been addressed. Only few therapeutic approaches suggest through tissue repair and regeneration. The most of treatment options aim to control the scar formation and adverse remodeling, while improving myocardial function. Of all the existing therapeutic approaches, the problem of cardiac tissue loss is addressed uniquely by heart transplantation. This review addresses the present state of research as regards stem cell therapy for CVD.

Introduction

Cardiovascular disease (CVD) is the foremost reason of morbidity and mortality. Progression and development of myocardial infarction and is a primary cause for heart failure. Present therapeutically strategies to treat infarcted heart and consequent heart failure comprise drugs (β -blockers and angiotensin, aspirin converting enzyme inhibitors), thrombolytic therapy, angioplasty, heart transplantation and ventricular assist devices. The relative incidence and death occurring due to MI are significantly increasing. As a result there is a need to identify novel therapeutic strategies. MI, in general considered as a heart attack, which occurs due to reduced blood flow or stopping of blood flow to a portion of heart that results in heart muscle damage. The most common

form of CVD is the myocardial infarction [1]. It is responsible for over 15% of mortality each year, among the vast majority of people suffering from non ST-segment elevation myocardial infarction (NSTEMI) than ST-segment elevation myocardial infarction (STEMI). The prevalence of myocardial infarction (MI) is higher in men in all age-specific groups than women [1].

More than 30% of individuals show atypical symptoms [2]. In women's chest pain may not be noticed but show symptoms of arm pain, neck pain, or feel tired [3]. In women above 75 years, 5% are affected with MI without any history of symptoms [4]. MI might lead to an irregular heartbeat, heart failure, or cardiac arrest. Based on World Health Organization (WHO), CVD are the major killers of people in recent times,



and it's basically because heart cannot renovate itself properly. Even if a person survives after the initial heart attack event, scar tissue renders the heart less effective at pumping blood and more likely to suffer future heart attacks.

In coming decades, in western world degeneration of cardiac tissue will be a key threat for mortality. Thus MI is going to be a health issue in coming years. Cardiac damage is linked with permanent loss and dysfunction of cardiomyocytes [5]. Currently, coronary artery bypass grafting, intervention, and drugs are used to partially recover from myocardial ischemia, yet these treatments are not enough to restore tissue damage occurred due to MI. Local decrease in the cardiocytes number in infarcted region resulted from increased oxidative stress in inflammatory microenvironment, scar tissue formation, tissue fibrosis and cardiac remodelling are the major reasons for higher rates of mortality due to heart failure after MI. Hence researchers and clinicians have started to find out newer therapies in treating heart failure resulted due to MI.

Coronary stent implantation, thrombolysis, coronary artery bypass grafting and pharmacotherapy are in current clinical use for treating MI to further enhance patients' survival. However these treatments couldn't able to meet up the fundamental requirements need to repair the injured heart and failed to restore the heart function. In these condition advances in regenerative medicine using stem cells has raised a scope for treating MI. Recently stem cell transplantation has showed a noteworthy evolution in preclinical as well as in clinical studies [6].

The regenerative ability of the adult mammalian heart is very partial, and this subsidizes to the widespread morbidity and mortality associated with CVD [7,8]. It has also become progressively outward that adult mammalian hearts do not anchorage endogenous stem cells of any physiological significance that can restore injured myocardium. Despite comprehensive research with numerous cell types over 15 years, stem cell therapy outcomes for cardiac repair have thus far been marginal at best.

Stem cells have long been examined as an answer, but despite their reformative progression in other parts of the body, they are not successful in matters of the heart. Introducing stem cells into the heart may cause difficulties, and it turns out that cardiac stem cells might not even exist. Several other investigators have done so much of research using stem cell "messengers" as an alternative, or converting other heart cells into beating heart cells.

Stem cell and regenerative medicine

Since 1990s, developmental biologists and embryologists had intensive research on the adult tissue stem cells because they are pluripotent progenitors and present in different tissues.

Stem cells majorly fall under two categories:

1. **Pluripotent stem cells:** Includes embryonic stem cell (ESC) and induced pluripotent stem cells (iPSCs) and their derivatives.

2. **Adult stem cells:** Includes hematopoietic stem cells (HSCs) and mesenchymal stem cells (MSCs) [9].

These are mesodermal in origin and are multipotent which resides in adult tissues and embryonic tissues. These are highly immune-privileged, have self-renewal capacity, low tumorigenic in nature and contain immunomodulation properties [10].

It was believed that adult tissue differentiation have the less probability to give rise to different lineages. This perception was swapped by the trans-differentiation concept; the one type of cells can give different lineage to other tissue or cell types [11]. Thus, these cells are believed to be capable for the treatment of various congenital deficiency diseases and regenerate injured tissues [11]. In the 1950s, researchers demonstrated that the bone marrow comprises of hematopoietic stem cells (HSCs) and mesenchymal stem cells (MSCs) that can generate the cartilage, fat, bone and cells can support the neovascularization [11].

Mesenchymal stem cells

MSCs compromise an innovative therapeutic tool for the treatment of heart diseases discharging a multitude of bioactive smidgens that ultimately leads to the improvement of tissues at sites of injury [12]. MSCs properties like immunomodulatory capacity, low immunogenicity, prevention of immune rejection, multi lineage differentiation (bone, fat, nerve cells, cartilage), self-renewal capacity puts them on high demand for clinical use in the era of regenerative medicine. MSCs can be obtained from various sources of tissues like fat, bone marrow, synovial membrane and muscle. From all these sources BMSCs are more widely used in clinical applications since their noticeable benefits.

Human Umbilical Cord Blood (UCB) as a source of MSCs

Human Umbilical Cord Blood (UCB) that make MSCs superior over other sources. Collection of UCB is non-invasive method unlike bone marrow [13,14], they can be efficiently cultured invitro. Collection of UCB does not have much ethical issues [15], cryopreservation of cells does not hinder the proliferation potential of UCB cells making them viable and long lasting [16]. For collecting UCB cells, generally a physician clamps the umbilical cord and makes a prick in the umbilical vein using a syringe and collects the blood into a bag containing nutrients and anticoagulants. The UCB is cleaned of infectious agents prior to cryopreservation and at last stored in blood banks for future utilization [16]. Harvested UCB cells can be effortlessly proliferated, and can be able to cultured invitro [17]. Additionally, cryopreservation of UCB enhances the quantity of mRNA retroviral receptor in cord blood and increases the ability to transduce retroviral vectors. Further this amphotrophic retroviral receptor appearance increases the efficacy of gene therapy since these receptors are major central targets in transduction of gene of interest [18]. In comparison with bone marrow UCB is considered as a richest source for progenitor cells and hematopoietic stem cells with increased proliferation potential [19]. There are several benefits to derive the stem cells from UCB such as



Human UCB serves as eminent source of stem cells and has a number of significant advantages over other stem cell sources.

First of all, non-invasive collection without any risk for the donor and a real abundance with more than 100 million births annually worldwide make the UCB a readily available source of stem cells.

UCB stem cells, unlike the more controversial embryonic stem cells, do not involve ethical issues.

UCB-MSCs do not develop teratoma when injected into the body.

Upon transplantation, these cells have potency to differentiate into the required cell types to provide the support in adverse conditions.

Although the cellular/tissue regeneration mechanisms of myocardial repair or improvement by transplanted UCB-MSCs has yet to be elucidated.

In recent times, researchers revealed that UCB comprises a smaller proportion of Very Small Embryonic-Like stem cells (VSELs) another form of pluripotent stem cells [20]. Recently, cell therapy has gained much attention as an alternative approach to treat various heart diseases. We are still in search of the optimal cell type for enhanced cardiac repair and regeneration.

A variety of cell types has been identified and utilized as a possible remedy to repair damaged myocardium. Reduced apoptosis has been noticed in case of hematopoietic progenitor cells [21,22]. It has been demonstrated that Human amniotic epithelial cells could be able to differentiate into cardiomyocyte-like cells after transplantation [23]. Enhanced cardiac function has been documented through the usage of MSCs [24-28], skeletal myoblasts, cardiac progenitor cells, endothelial precursor cells, skeletal muscle cells [29], and resident cardiac stem cells for treating Myocardial Infarction (MI) patients. Studies are being conducted on endothelial progenitor cells (EPCs) to enhance cardiac function in MI patients [30-33]. On the other hand still there is deviation with optimal cell graft intended for clinical applications. MSCs isolated from bone marrow of older patients when cultured in vitro exhibited lack of self-renewal, adhesion, proliferation, and integration into vascular tissue upon transplantation into damaged heart. Currently autologous transplantation is in wide applicability as this therapy circumvents graft versus host immune disease. But this autologous transplantation is not preferable in case of chronically ill and aging populations, where functional SCs number got decreased, restricting the recovery as well as repairing capacity of damaged tissue.

It has been identified that UCB cells inherit the capacity for repairing endothelial cells and muscle cells because of their angiogenic and myogenic properties, representing their suitability in repairing injured myocardium [9,14]. So far UCB cells presented extended track record for safety profile in efficient clinical transplantation [16]. Several properties of UCB

cells hold up the impression that they can provide better safety and efficacy in transplantation studies.

Several limitations prompts for discovery of most appropriate stem cell sources for utilization in transplantation of MI. Accordingly it was found that UCB cells as the most potential source of stem cells to rule out all these limitations that can be used successfully in transplantation with more benefits. When compared to autologous cells, number of UCB cells obtained is far higher which can be harvested non-invasively, contains the property of self-renewal and can be differentiated into multiple lineages. Most importantly these cells can withstand larger cryopreservation periods, exhibits minimal damage to other proteins and lower risk for losing protein signalling. It is necessary to achieve the survival of transplanted HUCB and its differentiation into endothelial cells or myocytes for promoting left ventricular remodelling. Still for attaining an efficient efficacy and stability of UCB cells for utilization in MI treatment there is a need to carry out many preclinical investigations as well as to reveal the underlying mechanism by which UCB cells help in myocardial repair [34].

Various Studies on Stem cells and CVD

MSCs are the have become most common cell type of choice that are being used in MI clinical trials (Table 1) [35], because of their immunomodulatory properties, multi differentiation potential, nutritional activity, abundant donor sources and safety [10,36]. MSCs shows low expression of MHC II and donot express of MHC class-I making them less immunogenic and will not elicit immune rejection during allogeneic transplantation [36]. Conversely, the therapeutic outcome of MSC transplantation is disappointing.

Huang, et al. 2019 [37], showed that combinatorial delivery of exosomes and stem cells in a sequential manner

Table 1: Clinical trials for the treatment of MI by MSCs transplantation.

| Phase | Dose (*10 ⁶) | Following up | Study |
|-----------|--------------------------|--------------|------------------------|
| Phase 1/2 | 20 | 12 months | Can et al. 2015 |
| Phase 2 | 150 | 6 months | Schutt et al., 2015 |
| Phase 2 | 100 | 12 months | Florea et al. 2017 |
| Phase 2 | 6 | 18 months | Gao et al. 2015 |
| Phase 1/2 | 180/220 | 24 months | Chullikana et al. 2015 |

effectively reduces scar size and restores heart function after Acute Myocardial Infarction (AMI). Delivery of exosomes into infarcted hearts 30min post (AMI) can significantly reduce inflammatory factors such as IL-6 and TNF- α , increase SDF-1 expression and angiogenesis, and promote stem cell survival in the stressed ischemic microenvironment at day 3 post AMI.

Only 3-10% of MI patients transplanted with MSCs showed an increase in Left Ventricular Systolic Function (LVSF) [38]. One of the reasons for this failure might be the inability of implanted cells for long term survival. Results showed that only around 3% of MSCs presence in marginal area of the infarcted



myocardium after 24 hours of systemic administration, it was even noticed that less than 1% of MSCs can able to survive for more than a week [9]. Current studies showed that paracrine mechanism plays a major role in success of MSC therapy in treating MI patients and it was even found that it is difficult to differentiate MSCs into cardiomyocytes [39].

BMSCs possess the ability of multidirectional differentiation, low high portability and lesser immunogenicity. All these properties of BMSCs make them as an ideal source of cells for utilization in cardiovascular disease therapies. In additions BMSCs express CXC chemokine receptor 4 (CXCR4) and chemotactic protein stromal cell derived factor 1 (SDF-1) enhances their automatic homing ability on infarcted area subsequent to transplantation [40-42], which finally helps in treating of cardiovascular disease.

The sequential events that occur after BMSCs transplantation into ischemic myocardium includes differentiation and fusion of BMSCs to cardiocytes and endothelial cells; paracrine effects associated with release of diverse cytokines like interleukin (IL)-6, platelet-derived growth factor, Vascular Endothelial Growth Factor (VEGF), Hepatocyte Growth Factor (HGF), Insulin-like Growth Factor (IGF), SDF-1 and Fibroblast Growth Factor (FGF) which plays a crucial role in restoring cardiac function. This is followed by mobilization of autologous progenitor cells or cardiac stem cells and promoting their proliferation and differentiation into cardiomyocytes for recovering cardiac function. Further the myocardium is protected by inhibiting inflammatory responses by decreasing the levels of inflammatory cytokines and gene expression. Several studies have shown that BMSCs transplantation in MI enhanced the differentiation of surrounding cardiocytes in infarcted area [43,44]. Further these transplanted BMSCs in MI enhanced angiogenesis, inhibited apoptosis, and exhibited anti-fibrotic properties and helped in significant improvement of myocardial repair in MI patients. Joint autologous BMSC therapy and shock wave has showed to be most effective than using in single [45].

Bone marrow stem cells (BMSCs) transplantation has revealed potential for cardiac regeneration [46], since within the microenvironment of the heart they can differentiate into cardiac cells [47-54], without making physical contacts with myocytes [48-53]. There may be probable elucidation is that one or additional influences secreted from myocytes stimulate BMSCs' differentiation into a myocardial phenotype. BMSCs may be provided by coronary artery infusion, and they travel to the site of injury and differentiate into myocardial cells in the damage tissue to progress heart function.

Conclusion

In summary, the potential usefulness of UCB derived stem cells is can be opted in preclinical settings due to readily available source, multipotent nature, immunologically naive and minimal ethical concerns. The success of this therapeutic strategy in preclinical models will facilitate the production and clinical applicability which has tremendous potential to save millions of lives each year with further understanding. Stem

cell based therapeutic approach may represent as an alternative promising strategy heart repair and therapy.

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