

Mesenchymal Stem Cells as a Potential Therapy for Cardiovascular Diseases: A Mini-review

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ABSTRACT

The abnormal structural and functional change in arteries, heart, veins and capillaries directly leads to different cardiovascular disorders (CVD), including atherosclerosis. The main objective of this review is to evaluate the use of stem cell research in the treatment of cardiovascular diseases. Annually more people die from CVDs than from any other cause. This disease remains the major cause of death in United States, while in low and middle income countries it is responsible for about 80% deaths. Annually almost 20% deaths worldwide take place due to CVD. The factors which contribute to this disease include age, systolic and diastolic blood pressure, environmental factors, smoking status etc. Most cardiovascular diseases can be prohibited by counseling about behavioral risk factors such as tobacco use, unhealthy diet, obesity, physical inactivity and harmful use of alcohol. Individuals who are suffering from this disease or those at high risk need early detection and management using counseling and medicine. Regeneration of damaged myocardium and treatment of CVDs can be achieved by great stem cell-based therapy. Traditional cell-based therapy is evolved in the totipotent cells, which is able to distinguish into various mature cells, forming functional tissue required for embryonic development. Other relevant new therapies that utilize pluripotent or multipotent (adult cells) are conceivable for making specialized mature cell lines.

Key words: Cardiovascular diseases, exosome, stem cell, therapeutic role.

INTRODUCTION

Cardiovascular diseases (CVDs) are a collection of disorders related to the heart and blood vessels. The ultimate result can be heart attacks or stroke which is mainly caused by blockage of blood flow to the heart or brain. Major CVDs are atherosclerosis, hypertension and aging (Dantas *et al.*, 2012). The other illnesses include; congenital heart disease, rheumatic heart disease, coronary artery disease, cerebral artery disease, ischemia and peripheral artery disease (Eakin *et al.*, 2010). The causes are generally the presence of a combination of risk factors. According to WHO (2015) report, CVDs are the number one cause of death

worldwide. Almost 7.6 million contribute to coronary heart disease (CHD) and stroke contributed to 5.7 million. It is observed that > 80% of the deaths appear in median income countries. The WHO predicts ~ 20 million CVD patients in 2015, considering for 30 percent of all deaths globally (Bryce *et al.*, 2005). It has been predicted that non-transmissible diseases will be the cause of more deaths in developing countries than in the developed countries by 2050. CVD singly will be answerable for extra extinction or death in power earning nations than contagious disorder (involving HIV/AIDS, malaria and tuberculosis), parental and maternal and nourishment disease merged (Beaglehole and Bonita, 2008). Hence, cardiovascular disease has become, the popular major alone attribute to world mortality and will stay predominate mortality movement in future. Since 1970 many developed countries have been

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found with low rate while developing with high rates (Thygesen *et al.*, 2012). According to American heart association (AHA) statistical report (2016) prevalence of cardiovascular health behavior in the United States varies from <1% for healthy diet pattern to >80% for smoking and blood pressure among the children and 1.5% for healthy pattern to up to 78% among the adults.

Dynamics of cardiovascular disease

CVD is a multifactorial disorder showing large diversity of phenotypes. The list of factors that contribute to CVD can be categorized into classes.

Age related physiological change

Age is a powerful chance for essentially all kinds of CVDs, basically heart failure, hypertension, coronary artery disease and stroke are fundamental widespread that arise systematically with age. The diseases arise from 12.8% in men and 10.1% in women in age range of 20- 39 year to 83% in men and 8.1% in women in age group of 80 years or above (Go *et al.*, 2014). Cardiovascular changes in older ages are characterized by endothelial dysfunction, arterial stiffness and degenerative changes of endocrine system. Table 1 shows many such changes with respect to organ involvement and with occurrence of different cardiovascular diseases. Age associated changes occur all over the body and in essentially all organ processes.

Hemodialysis

CVD is the major cause of death during hemodialysis. Among the cardiovascular causes sudden cardiac death (SCD) is most common. Major causes of SCD are the rapid fluid and electrolyte shifts during hemodialysis, endothelial dysfunction, myocardial interstitial fibrosis and low myocardial tolerance to ischemia in dialysis patients (Hou *et al.*, 2012). The prevalence of cardiovascular disease is high in the patients receiving hemodialysis (Katia *et al.*, 2015). It has been studied that, in hemodialysis receiving population, the CVDs occur at earlier age and develops quickly developed then in general population (George *et al.*, 2007).

Genetic factors

Genetic factors are also reported as major cause of developing CVDs. From the family

combination genetic factors are responsible for developing CVDs (Wang *et al.*, 1996) Genetic, epigenetic and exosmic techniques are used to improve the quality of patients' life, while the contribution of modified medicines in CVD treatment is also appreciable. Analogous phenotypic evidences are crucial for detailed understanding of the interaction between disease and genes, as well as the role of various extrinsic factors on different genotypes for the accurate consequences. This complexity also contributes to difficulties in diagnosis and prognosis of the disease (Ramsey *et al.*, 2011).

Information of molecular processes related to cardiovascular diseases can improve medicinal therapy on wide basis despite of genotype of individuals or specifically targeted to the genotype. Many of cardiovascular loci have been discovered during the past few years. CVD are associated with modifications in the DNA sequence and their specific pattern of inheritance. The risk of CVD transmission to baby may be as high as 50 percent with the changes in cardiovascular conduction, aberrant function and structure, and vascular biology. Mutation in single cardiac gene has been reported in many individuals of all ethnic groups and concludes in mature cardiovascular death and morbidity. Genetic mutations of cardiac specific genes (TGFB2 and NKX2.5) cause the deformity of ventricular and arterial division (Mizuguchi *et al.*, 2004).

Cardiomyopathy or myocardial dysfunction is caused by gene mutation in intersectional myocytes (heart muscles cells). Arrhythmogenic disease is caused by the several mutations in the genes that encode cardiac ion channels and structural proteins. Molecular representation permits analytic appearance and identification of gene-specific phenotype. Approximately 35% of trials showed more than 70 mutations in beta myosin heavy chain encoding gene (MYH7). Hypertrophic cardiomyopathy is caused by more than one gene because it is a heterogeneous defect (Roberts *et al.*, 2013).

Environmental factors

Multiple evidences show that environmental factors are associated with incidence and severity of

Table 1: Age-associated changes in cardiovascular system with involved organs.

Age associated changes	Organ involved	Cardiovascular Disease
Increased intimal thickness	Vasculature	Systolic hypertension
Arterial stiffening	Vasculature	Coronary artery stenosis
Increased pulse pressure	Vasculature	Peripheral artery stenosis
Increased pulse wave velocity	Vasculature	Carotid artery stenosis
Increased left arterial size	Atria	Atrial fibrillation
Decreased maximal heart rate	Sinus node	Sinus node dysfunction ,sick sinus syndrome
Increased conduction time	Atrioventricular node	Second, third –degree block
Sclerosis, calcification	Valves`	Stenosis, regurgitation
Increased left ventricle wall tension	Ventricles	Left ventricular hypertrophy
Prolonged early diastolic filling rate	Ventricles	Heart failure (with or without systolic dysfunction)
Ventricle premature complexes	Ventricles	Ventricular tachycardia, fibrillation

CVD. Exposure to different environmental conditions contributes to the development and extremity of cardiovascular disease (Kristen *et al.*, 2015). Changes in environment (Migrant studies) have showed significant CVD risk in genetically stable populations. Nutritional and lifestyle choices can also affect CVD risk. Environmental toxicants also influence CVD which is suggested by recent studies in the field of environmental cardiology. Revelation to tobacco smoke associated with increased cardiovascular morbidity and mortality is core example of such environmental risks. Scientific experiment on animals has shown that exposure to the tobacco smoke induced endothelial dysfunction and prothrombotic responses and aggravate atherogenesis and myocardial ischemic injury (Toole *et al.*, 2008). Several large population-based studies indicated that air pollution increases CVD morbidity and mortality. Polyaromatic hydrocarbons, aldehydes, and metals have also been reported to upraise CVD risk by affecting atherogenesis, thrombosis, or blood pressure regulation. When several drugs, toxins, and infection were introduced in maternal body, they cause cardiac birth defects and premature CVD. Negative emotions also chronic environmental stress is also an important contributing factor in induction of CVD risk (Lage *et al.*, 2012).

Infection

Atherosclerosis is a major cause of cardiovascular infection (Alie *et al.*, 2015). Bacterial species such as spirochetes *Borrelia burgdorferi* and flagellated bacteria such as

streptococci have the potential role in development of atherosclerosis. At severe stage fibrinogen, high sensitivity C-reactive protein (CRP) and identification of vascular wall infection, tumor necrosis factor alpha (TNA- α) are biological markers of cardiovascular disease. Each indicates the chance of future development of CVD leading to myocardial infarction and stroke. Procedure of inflammation showed potent communication between cardiovascular pathology, chance to high blood pressure, cholesterol levels and metabolic condition such as diabetes, obesity and resilience to insulin and behavioral characteristics like exercise and smoking (Ndumele *et al.*, 2011).

The capacity of gram negative bacteria on the function and structure of artery has been considered by Wiedermann *et al.* (1999) that show a relationship between endotoxemia and carotid atherosclerosis in a community-based education. The major and important endotoxin receptor is a link between dissolvable blood level CD14 and aortic rigidity (Amar *et al.*, 2008). Human blood microbiome information illustrated that gut microbiota dysbiosis p lay a vital role in many disorders *e.g.*, Type 1 diabetes. To analyze the mode of action of some microbes, it is needed to research the effects of microbiota equanimity on the starting site of cardiovascular disorder with an emphasis on proteobacteria phylum in a habitual population (Amar *et al.*, 2013).

Therapeutic development using stem cell therapy

There are two basic concepts of stem-cell based therapy. (a) Traditional cell-based therapy has

been evolved in the totipotent cells, which is able to differentiate into various mature cells forming functional tissue required for embryonic formation. (b) Other relevant therapy utilizing pluripotent or multipotent adult cells is conceivable for making specialized mature cell lines. With the discovery of induced pluripotent stem cells (iPSC) it becomes easy to cure degenerative diseases and other diseases which has limited therapeutic options (Methews *et al.*, 2015). Stem cell-based strategy can be applied to reform, alter, repair, cure or disturb the malignancy of tumor by treating patients with Peripheral vascular disease and Right heart failure to motivate the tissues at the molecular and cellular level to regenerate. Endothelial progenitor cells (EPCs), found in the bone marrow have the ability to differentiate into endothelial cells. Endothelial nitric oxide synthetase (eNOS) organized EPCs apply to stop the infection and repair microvasculature (Lee *et al.*, 2013).

Regeneration of damaged cells by stem cell-based therapy

Regeneration of damaged myocardium and treatment of CVDs is exhibit by great stems cells-based therapy. The ideal sources of stem cells-based therapy are adipose tissue-derived stem cells, induced pluripotent stem cells (iPSCs), embryonic stem cells (ESCs), mesenchymal stem cells (MSCs), and endothelial progenitor cells (EPCs). These cells have indication of therapeutic potential on CVDs (Schussler-Lenz *et al.*, 2016). Especially MSCs contain multipotent differentiation ability and paracrine activity and also have the ability to differentiate into osteoblasts (Rust *et al.*, 2007) adipocytes (Morganstein *et al.*, 2010), chondrocytes (Zhang *et al.*, 2011), cardiomyocytes (CMCs) (Kawada *et al.*, 2004), endothelial cells (ECs) and (VSMCs) vascular smooth muscle cells (Silva *et al.*, 2005). The MSCs transplantation has been demonstrated as an advanced and favorable therapeutic application for CVDs.

The MSCs basically originate from ectoderm and mesoderm throughout early embryonic development, and also found in many type of tissues and organs like fat, muscle lungs, pancreas, bone marrow, liver and synovial membrane (Vos *et al.*, 2012). It has been generally identified that inoculate

MSCs differentiated into CMCs and partially for therapeutic effects of MSCs transplantation. MSCs also differentiate into VSMCs and ECs, which participate in revascularization (Kurpinski *et al.*, 2010; Wang *et al.*, 2014).

MSCs also have the ability to revascularize the cells and CMCs in the myocardial infarction (MI) and also upgraded the cardiac function of damaged heart (Quevedo *et al.*, 2009). Only a minimum MSCs survived and engrafted after transplantation, MSCs also can secrete functional paracrine factors for example basic fibroblast growth factor, insulin-like growth factor-1, vascular endothelial growth factor (VEGF) and to produce different immune effects such as promoting vascular regeneration, repairing damaged kidney, making myocardial repair possible and improved cardiac remodeling (Haider *et al.*, 2008). Mesenchymal cells have the ability to differentiate into mesoderm, immuno-modulatory function and play a role in maintaining and replenishing the endogenous stem cells (Vasileios *et al.*, 2015).

The murine hind-limb ischemia preparation is a model of peripheral arterial disease (PAD), and is useful for testing new therapies or remedy. MSCs repair different type of tissues after damaging and are recently being applied in clinical experiments to cure person with CVD. The specific mechanism and the capacity of myocyte regeneration in angiogenesis is still ill defined (Aguirre *et al.*, 2010).

Large amount of MSCs were introduced in 20 patients with ischemic heart disease at the time of surgery for myocardial revascularization. Actual fact was that MSCs have the ability to revascularize the damaged heart muscles and differentiate into endothelial and smooth muscle cells developing remarkable left ventricular and also have tendency for decreased fibrosis and increase vascular density (Silva *et al.*, 2005).

Exosomes secreted by MSC's

It has been demonstrated that transplanted MSCs may secrete abundant particles known as exosomes, which can minimize tissue damage and also improve tissue repair. Exosomes are cholesterol containing phospholipid vesicles enriched with micro-RNAs (miRNAs) which can well regulate

gene expression in a post-transcriptional process and play a vital role in different pathological processes. They are nano-sized membrane vesicles with 30-100nm diameter and originate from multivesicular endosomes and excreted with the help of cells into exterior environment of the cell. There are multiple contents in exosomes containing protein, lipid, cytokines, mRNA, miRNA and ribosomal RNAs (Jenjaroenpun *et al.*, 2013).

Exosomes have influence on cardiovascular system, it is suggested that exosomes secreted by MSCs will be considered as a classical therapeutic mark for CVDs in near future (Li *et al.*, 2012). Stem cells have their therapeutic potential mainly through a paracrine mechanism other than trans-differentiation, and exosomes have emerged as an important paracrine factor for stem cells to reprogram injured cells (Guo *et al.*, 2015).

EFFECTS OF EXOSOMES ON CARDIOVASCULAR SYSTEM

Angiogenesis

Adipose MSCs excretes exosomes and micro vesicles, and also has potential to control angiogenesis (Lopatina *et al.*, 2014). Moreover, vaccination of exosomes from MSCs into stroke rats could diminish the symptoms through controlling angiogenesis. MSCs exosomes through the miR-16-mediated down regulation of VEGF (vascular endothelial growth factor) generate a compelling inhibition of angiogenesis. MiRNAs-bearing endosomes are easily incorporated into CMCs, and ECs giving rise to cardiomyocytes protection and angiogenesis advancement (Weber *et al.*, 2013). The MSC-derived exosomes down-regulated the expression of vascular endothelial growth factor (VEGF) in tumor cells, thus suppress the angiogenesis (Lee *et al.*, 2013). There are many researches that revealed significant roles of miRNAs enclosed in exosomes in the progress of CVDs.

Anti-apoptosis

Myocardial infarction is distinguished by continuous loss of cardiomyocytes (CMCs) therefore resulting in congestive heart failure, then become a tough task because of the collapse of CMCs to exchange apoptotic cells.

Exposure and prominence of MSCs offer an innovation for MI therapies because of their potential to instantly discriminate into CMCs and their anti-apoptotic effect from paracrine action. MSCs have capability to promote ischemic CMCs damaging by shifting miR-22 in exosomes targeting methyl CpG binding protein 2 (MeCP2) to minimize apoptosis.

Anti-cardiac remodeling

Cardiac remodeling or cardiac alteration, improved outcomes of CVDs like myocardial hypertrophy and fibrosis, commonly results into heart failure due to lack of regular therapy and proper treatment (Haizlip and Janssen, 2011). MSCs transplantation minimized clog size, develop left ventricular ejection fraction and also change remodeling after persistent myocardial infarction. Recently research revealed that exosomes derived from MSCs are able to enhance myocardial activity and inhibit disadvantageous remodeling after restore blood flow through blocked arteries typically after a heart attack. In thrombolytic therapy via activating pro-survival signaling, not only rehabilitating bioenergetics but also minimizing oxidative stress. After all anti-cardiac remodeling consequences of MSCs-derived exosomes were accepted but appliance of exosomes mediated insurance have not been authentic or proved (Arslan *et al.*, 2013).

Cardiac regeneration

Necrosis and apoptosis of CMCs because of therapeutic microenvironment or injured factors is ready to heart failure. MSCs have ability to differentiate into multiple lineages like cardiomyocyte cells *in vitro and vivo* thus used in improving the myocardium function and injured myocardium (Shen *et al.*, 2015). Cardiac regeneration by MSCs and cardiac stem cells (CSCs) differentiation is heightened as a policy for healing CVDs (Sassoli *et al.*, 2011). MSCs are capability to promote endogenous cardiac regeneration Micro vesicles and exosomes secreted by cardiomyocytes progenitor cells (CPCs) can lead to cardiac regeneration and give improvement to cardiac function by promoting migration of ECs and secretion of VEGF resulting in angiogenesis. The mixture of human MSCs and human cardiac stem

cells have a good effect on the decreasing of infarct size and improve cardiac consequences than MSCs (Sabin and Kikyo, 2014). Although, even if exosomes participate in cardiac regeneration of MSCs still remains ambiguous, and the activity of exosomes in cardiac regeneration requires more analysis.

Use of stem cells in production of bio artificial organs

Tissue engineering illustrates that a prospective area of research in which a lot of cells, scaffold or bioreactors are employ to manufacture to produce copy, exchange or reformation of faulty tissue or organ. Bio artificial organ (heart) is now possible to regenerate or repair by artificial heart muscle (AHM) which is composed of neonatal rat cardiac myocytes, fibrin gel, de-cellurized scaffold and can construct by manipulate adult rat heart to a string of de-cellurization solution. By stitching the artificial heart muscle to outer part of the de-cellurized heart and culturing. As a result, bio-artificial hear display victorious de-cellurization of the scaffold and adjacent cell with rich artificial heart muscle outside the perimeter of heart.

The capability of cardiac regeneration in young mammals is spectacular while the heart of children is more capable for cardiac regeneration for example after surgery the left coronary artery originates from pulmonary artery or with univentricular heart in children (Risbud and Bhonde, 2001).

Regeneration therapies involve bioengineering tissue transplantation and cell insertion. Cell sheet based tissue transplantation engineering technology is most popular treatment recently accessible for heart failure is heart transplantation (Sekine *et al.*, 2012).

Human induced pluripotent stem cells (iPS) are distinguished into cardiomyocytes to create cardiomyocytes sheets. Firstly, three layers of iPS cardiomyocytes (hiPSCM) sheets transported on tissue of naked rats. Then, invent thick tissue and three layers of sheet are transferred on one day, furthermore three-layers of sheet transferred to on given day after the initial sheet is changed. On the third day the final three layers of sheet are again transplanted or transported, making nine layers. In

the final step six layers of sheets are transferred to on fat tissue which combined with arteries and veins to create transportable bud with communicable vessels (Komae *et al.*, 2015)

The regeneration of tissue damage or lost due to tumor or disorder is thought a model for regenerate or to repair in this case donor deformities appear in different part of the body. In recent years molecular and cellular techniques of healing and possibilities for regeneration have been established. Cell based technique in which Mesenchymal stem cell (MSC) from adipose tissue is mostly used which leads to good healing outcome with reduced donor site morbidity. For example, growth factor based approaches or platelet-rich plasma attains excellent result in the area of bone healing and wound (Kuhbier *et al.*, 2015).

CONCLUSION

The latest therapies in cardiovascular medication goal are to stop death rate and upgrade patient status of life. From the last few decades, mortality rate of CVD have reduced appreciably because of the recent development in medical diagnosis and promote healthcare. Tissue engineering approaches for the treatment of cardiovascular disease keep meaningful promise for new therapeutic techniques. Further work on different stem cell techniques are needed to investigate for CVD treatment. These could lead to the better approved option for heart valve, revascularization, repair arrhythmias and congenital malformations.

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