Stem Cell Treatment Of Cardiac Diseases

Abstract

Cardiovascular diseases cause worldwide death in mainly middle-income and low-income countries. There is a natural ability of different organisms in which the heart muscle shows natural regeneration in many ways. But in severe condition, the natural mechanism cannot able to regenerate the heart muscles (cardiomyocytes) so in severe conditions, the accurate therapy of these cardiovascular diseases is only a heart transplant but this treatment is very expensive. The recent cell-based clinical trials show that cell-based therapy also has the potential to treat heart disease. These cells are the stem cells are the cells that have the ability to differentiate into any other type of cells. The stem cells are present in many parts of our body like bone marrow, heart, kidneys. These are of many types depending upon the harvesting of these cells from their sources like embryonic stem cells. In this review, it is shown which type of stem cells are used as the best source of cardiac therapy. Clinical trials are done on using many sources of stem cells for cardiac treatment. The indigenous heart stem cells have been shown to differentiate into multiple types of cells present in the heart including cardiac muscle cells also used for cardiomyocytes regeneration. So with the help of new findings, cardiovascular diseases can be prevented or treated by using stem cell therapy.

Keywords

Stem cells, cardiomyocytes,

Introduction

Cardiovascular diseases are disorders of the heart and blood vessels and include coronary heart disease, cerebrovascular disease, rheumatic heart disease, and others .cvd takes the lives of 17.9 million people every year due to an unhealthy diet, use of alcohol, and physical inactivity (who).in Pakistan the 30-40% of death are due to CVD .heart failure leading cause of death worldwide including low income and middle-income countries(Perin and Silva 2004; Karantalis and Hare 2016; Thorning et al. 2016) others causes of heart diseases are due to high blood pressure and also by the gradual loss of cardiomyocytes.it is also caused by consuming high-fat dairy products(Thorning et al. 2016). The only stranded therapy for heart failure that addresses the fundamental problem of cardiomyocytes loss is cardiac transplantation. The new discoveries on the regenerative ability of stem cells and progenitor cells for treating and preventing heart failure have transformed experimental research and led to an explosion in clinical investigation. The ultimate goals of cell therapy are myocardial regeneration &neovascularization leading to clinical improvement without severe adverse effect

Stem cells

Stem cells are cells that have the ability to differentiate into specific cell types. The stem cells have 2 defining characters 1-renewal to produce progeny exactly the same as the originating renewal and the ability to differentiate a special adult cell type (Idowu 2016)

Cardiac regeneration capacities invertebrates

Mammalian heart

It is agreed that the regenerative capability of human cardiomyocytes is not enough to compensate for the loss during myocardial diseases. Dedifferentiation of cardiomyocytes near the injured zone occurs before their proliferation and is characterized by loss of cardiac contractile proteins such as a-myosin heavy chains and troponin T. it is shown that the mammalian cardiac muscle regeneration shows a poor ability of adult mammalian cardiomyocytes to enter the cell cycle and divide(Kikuchi and Poss 2012). But in fetal the cardiomyocytes DNA replications occur without cytokinesis in injured rodents' ventricles the detectable DNA replication in the nuclei of myofibers bordering necrotic tissue was detected by incorporation of H-thymidine.

Amphibian’s heart

The natural cardiac generation capacities have been shown in frogs, salamanders are the champions of regeneration among vertebrates as they are able to renew the removed or injured parts. the regenerative capacity of amphibian hearts has varied. in the new heart, the eventual formation of connective scar tissue appears to be the dominant response after resection of the ventricular apex and there is only minor replacement of cardiac muscle (oberpillar1947) zebrafish also show cardiac regeneration response (Kikuchi and Poss 2012).

Teleost hearts

The zebrafish has become a popular model system for understanding vertebrate embryonic development. So this popularity has encouraged the exploration of its regenerative capacity. zebrafish has the ability to regenerate many structures such as retinae, brain tissue spinal cords (Kikuchi and Poss 2012). In one study of new approaches to study the regenerative capacity of zebrafish WANG ET AL(2011) generated a transgenic system to facilitate cell-type-specific ability in zebrafish this system involves two transgenes (a) 4-hydroxytamoxifen (4-HT)-inducible Cre recombinase restricted to cardiomyocytes by regulatory sequences of cardiac myosin light chain2 (cmlc2), (b) a cytotoxic DTA (diphtheria toxin A chain)genes that can be inducibly targeted to CreER expressing cells. When in these fishes single injection of 4HT causes a 60% loss of cardiomyocytes throughout the heart. It is a massive loss in which the heart cant survive and change many of its working .but this process reversed within a few days. the recovery of cardiomyocytes was detected in the ventricle and by 30 days it was filled with new muscle tissues and show little or no new scar tissues. (Kikuchi and Poss 2012)

Mechanisms that stimulate myocardial regeneration

Organ wide injury responses

All major cardiac tissues (epicardium, endocardium, and myocardium) show heart regeneration in response to any injury. (Kikuchi and Poss 2012). The early response is shown by the endocardium. After about an hour in local injury the endocardial cells throughout the heart show detachment from underlying myofibrils. then it induces the expression of two developmental marker genes raldb2 and begs (Kikuchi et al. 2011b lkhna hy) similarly embryonic epicardial

markers are formed as early as one day after injury and become detectable around the entire heart. Lepilina et al. 2006. in the myocardium, gata4 genes is activated in ventricular cardiomyocytes which are located in the subepicardial compact layer of the entire ventricles in seven days after injury.

Regulation by nonmyocardial cells

During heart regeneration in zebrafishes, the epicardium and endocardium play important roles in signaling and structural roles. as indicated earlier morphological changes in endocardial cells start organ-wide but become localized to the wound area by approximately one DPA.the endocardial cells and epicardial sites near the injury sites integrated into the wound maintain high expression of raldb2 while regeneration continues. Recent transgenic experiments involving overexpression of dominant –a negative form of RA receptor or an RA degrading enzyme indicate that the RA produced by the activation of endocardial and myocardial cells is essential to the maintenance of myocardial proliferation at the injury site. (Kikuchi and Poss 2012) (Kikuchi et al. 2011b). During zebrafish heart generation multiple developmental signaling pathways have been functionally implicated. As epicardial cells appear to facilitate the new vascular components during embryonic heart development.

Cardiomyocyte dedifferentiation

Proliferation by resident cardiomyocytes is the primary source for regeneration in adult zebrafish and mouse hearts. Cardiomyocytes dedifferentiation is typically characterized by the reduction of the sarcomere structure and expression of fetal gene markers and it shows the shared mechanism associated with cardiac muscle regeneration. So how the dedifferentiation is initiated. the dedifferentiation characters are detected in the adult mammalian heart under some pathological situations (Kikuchi and Poss 2012)(Dispersyn et al.2002, Driesenetal.2009, R¨ucker-Martin et al. 2002, Sharov et al. 1997) the understanding mechanisms that underlie these changes may provide a clue to identifying molecules that induce cardiomyocyte dedifferentiation.

Stem cells used for cardiac therapy

Different types of stem cells can be used for cardiac treatments due to their ability to differentiate into cardiomyocytes. the different experiment was done to see the ability of the type of stem cells which can be used for the cardiac treatment

1. Human mesenchymal stem cells

Human mesenchymal stem cells are thought to be multipotent cells(which have the ability to give rise to many but limited cells). bone marrow is the major source of adult hematopoietic stem cells.2which contributes to the regeneration of mesenchymal tissues such as bone cartilage, muscle ligament, tendon and adipose.3-5mscsinvolve in all organ homeostasis, wound healing. These cells have the ability to transdifferentiate into adult myocardium. in this experiment, a small bone marrow aspirate was taken from the iliac crest of healthy human volunteers and then from the bone marrow the human mesenchymal stem cells were isolated .then they labeled these cells with lac z and then inserted them into the left ventricle of CB17 SCID/beige adult mice by using adenovirus as vector .after 1-week different cardiac proteins

were detected .which shows that the purified hMSC from adult bone marrow has the ability to differentiate into cardiomyocytes. (Williams and Hare 2011)

In another experiment done by Lan Luo et al. they used synthetic analogs and test their therapeutic potential for the treatment of acute myocardial infarction in mice. They packaged secreted factors from human bone marrow-derived mesenchymal stem cells into poly (lactic-co-glycolic acid)microparticles and then coated them with MSC membrane. They named these therapeutic particles synthetic MSC. Syn MSC contains factor release profile and surface antigens as similar to the genuine MSC. synMSC promoted cardiomyocyte functions and displayed cryopreservation and lyophilization stability in vivo and in vitro. In a mouse model of acute myocardial infarction, direct injection of synMSC promoted angiogenesis and mitigated left ventricle remodeling. The result shows that the synMSC were successfully fabricated and demonstrated its regenerative potential in mice with acute myocardial infarction(Perin and Silva 2004; Thorning et al. 2016; Luo et al. 2017)

2. Skeletal myoblasts

The skeletal myoblast is injected into the ischaemic myocardium(Menasché 2007) was the first cell-based cardiac generation strategy. The myoblast is resistant to ischemia and can differentiate into myotubes in vivo but not can differentiate into the cardiomyocytes(Perin and Silva 2004; Laflamme and Murry 2005) and improve ventricular function in laboratory animal experiments(Menasché 2007). Myotubes do not integrate electrically with surviving cardiomyocytes. (Laflamme and Murry 2005). Due to the lack of efficacy of skeletal myoblasts(Cleland et al. 2007) in humans, they are restricted and it is unlikely that skeletal myoblasts will be able to truly regenerate myocardium. Mouse skeletal muscle contains a non-satellite population that has the ability to differentiate into beating cells. (Perin and Silva 2004; Winitsky et al. 2005)

3. Bone marrow-derived cells

4. Endogenous cardiac stem cells

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