Review Article

Jour Cas Stu Cas Rep, 2(2), 2023, 16-21

Journal of Case Studies and Case Reports

Open access peer reviewed international indexed journal Online ISSN: 2583-4428

Content Available at www.saap.org.in

CURRENT SITUATIONS AND FUTURE OF STEM CELLS IN CARDIO VASCULAR MEDICINE

Lingala Yaswanth*,Dara Shalem Raju, Balabadrapatruni. Sai Keerthana and Chandu Babu Rao.

Priyadarshini Institute of Pharmaceutical Education and Research, 5th mile, Pulladigunta-522017, Guntur, Andhra Pradesh. India.

Received: 14 July 2023 Revised: 22 July 2023 Accepted 27 Aug 2023

Abstract

Presently available treatments for cardiovascular disease only serve to postpone the illness, which is the primary cause of death globally. Cell-based therapies may be able to enhance heart function, according to current clinical trials and laboratory studies. This has exciting implications for cardiac regeneration. The capacity of stem cells to self-heal, regenerate physiologically, and improve impaired functional organs or tissues is remarkable. For heart repair, two different cell types can be employed: somatic stem cells and allogeneic stem cells. In order to restore blood flow, progenitor cells and other progenitor cells can develop into different types of vascular cells. The heart is not terminally differentiated, as evidenced by more recent studies showing local cardiac stem cells to differentiate into a variety of heart cell types, including cardiac muscle cells. The only thing that present treatments do, meanwhile, is slow the development of heart failure; they do not promote regeneration to make up for the loss of functional myocytes. With the potential to treat ischemic cardiac injury and heart failure, stem cell-based therapy is a revolutionary approach in which cardiac tissue is regenerated to improve cardiac function and lower patient morbidity and death. Potential sources of cardiac-specific stem cells will be covered, including mesenchymal, resident cardiac, embryonic, and survival in injured myocardium. Additionally, cardiac stem cells will be integrated into tissue patches and methods for generating bioartificial myocardial tissue and entire organs will be covered.

***Keywords*:** Cardiovascular disease, Stem cell, Cardiomyocytes, Coronary Artery Disease; Myocardial Infarction; Heart Failure.

***Corresponding Author**
KLingala Yaswanth

doi: https://doi.org/10.37022/jcscr.v2i2.601

Introduction

In all societies, cardiovascular disease (CVD) is the leading cause of morbidity andmortality, and it is in expected that the incidence of CVD will increase in the future. Currently, many cardiac treatments are available, including drug-based revascularization, medical device implantation, and surgery, e.g., heart transplantation (3). However, for heart conditions that are difficult to cure, such as ischaemic heart disease and congestive heart failure, more plausible treatments are still urgently needed. The focus of regenerative medicine has been on delivering new stem and progenitor cells, using differentiated cells to replace lost and damaged cells, stimulating endogenous tissue-residing stem cells, and promoting impaired cardiac function for the healing of damaged cardiac tissue. Progenitor cells produce new cells and lead to the migration of angiogenic or immunoregulatory cells to stimulate the repair process, and bioengineered or plastic tissues or whole organs can be used to replace some or all of the heart. However, cell-based therapies are the most favourable for clinical regenerative medicine because, in the past decade and a half, cell-based therapies have been

tested in many clinical trials in the treatment of CVD. In the field of biomedical research, stem cell methods have developed the fastest, with the aim of not only helping maintain tissue and organ homeostasis during growth and development in the prenatal and postnatal periods but also helping restore the normal state after tissue damage or injury. Many types of differentiated progeny can be produced by stem cells, and additional stem cells can be produced via self-renewal [5]. despite stem cell composing a small part of tissue, some rare stem cells, such as bone marrow stem andprogenitor cells, still participate in tissue regeneration; similarly, stem cells in the heart may participate in the regeneration of cardiac tissue after injury. The only standard therapy for heart failure that addresses the fundamental problem of cardiomyocyte loss is cardiac transplantation. New discoveries on the regenerative potential of stem cells and progenitor cellsfor treating and preventing heart failure have transformed experimental research and led to an explosion in clinical investigation.

Stem cells for CVD therapy

A very exciting therapeutic strategy is to regenerate cardiac tissue by replacing lost cells or rejuvenating damaged cells. In fact, stem cell- based therapies for cardiac regeneration canbe used to cure CVD in a manner

that traditional medicines and newer biological therapies still cannot, even though they are used as established treatments for cardiac damage and heart failure. Cardiac cell-based therapy has been performed with a wide variety of cell types, including aspirated bone marrow cells, peripheral blood progenitor cells, stem cells, cells expanded through ex vivo culture, pluripotent stem cells (PSCs), skeletal myoblasts, and endothelial pro genitor cells, such as embryonic stem cells (ESCs). (3)

1.1 Cardiac Myocytes [CMs]

CMs are the cardiac myocytes which are also called as heart muscle. cardiac muscle contain cells that expand and contract in response to electrical impulses from the nervous system these cardiac cells work together to produce the rhythmic, wave like contractions that is the heart beat.

2 Cell Sources

2.1 Mesenchymal stem /stromal cell

Mesenchymal stem/stromal cells (MSCs) reside in the bone marrow stroma and can differentiate into osteoblasts, chondrocytes, and adipocytes. In addition, MSCs differentiate in vitro into spontaneously beating cardiomyocytes (CMs) after exposure to the demethylating agent 5-azacytidine. Because of their cardiomyogenic potential, MSCs have been transplanted in animal models of myocardial infarction (MI) Another advantage of MSCs for the repair of dam aged myocardium is their ability to suppress immune rejection and curb the inflammatory response.

.Cardiac Stem Cells

Since the 1960s, studies of CM proliferation in rodents had indicated that the adult mammalian heart was a terminally differentiated, postmitotic organ without the capacity for cellular regeneration. Over the past 10 y, however, several findings have challenged this view. Observation of cell division, telomerase activity, telomere shortening, and CM apoptosis haveprovide evidence of CM turnover in adult human hearts (14) Recently, Porrello et al. showed that the hearts of 1-d-old neonatal mice can regenerate after partial surgical resection, but this capacity is lost by 7 d of age . The most compelling evidence for CM renewal in maintaining cardiac homeostasis comes from a study in which the amount of 14C (generated from above- ground nuclear testing between 1955 and 1963, before the implementation of the Limited Nuclear Test Ban Treaty) integrated into the DNA of human myocardial cells was used to date the birth of myocardial cells (3)

2.2 c-Kit and stem cell antigen-1 as markers of cardiac progenitors

Detection of the Y chromosome in undifferentiated cells and differentiated CMs found in female donor hearts transplanted into male patients not only supports the concept of cardiacchi merism in humans but also suggests the existence of cardiac progenitor cells that give rise to new CMs. This putative stem cell population was positive for surface antigens c-Kit/ CD117 and/or multidrug resistance-like protein 1, or stem cell antigen-1 (Sca-1) Side population cells

Side population (SP) cells, known for their ability to efflux vital dyes such as Hoechst 33342, were initially discovered as hematopoietic stem cells (5). ATP-dependent transporters, including multidrug resistance-like protein 1 and ATP-binding cassette subfamily G member 2(ABCG2), are believed to mediate dye exclusion, and both ABCG2 and multidrug resistance- like protein 1 have been cited as molecular determinants of cardiac SP cells in the adult myocardium. Direct injection of heart derived Sca-1+/CD31− cells into the peri-infarct region immediate following MI in mice limits left-ventricular remodel, attenuates contractile dysfunction, and improves myocardial energy metabolism

2.3 Cardio spheres

Cardio spheres present another potential source of endogenous cardiac stem cells. Cardio sphere cells are derived from cultured explants of mouse hearts and human atrial or ventricular biopsy samples following gentle enzymatic digestion. (15) They are able to migrate over the adherent portion of the explanted tissues. Have shown that the Sca-1+ subpopulation of cardio sphere cells preferentially expressing precursors that give rise to second heart field structures. Of particular note, the yield of cardio sphere cells from injured hearts is greater than from uninjured hearts, and cardio spheres are easily isolated and expanded from “middle aged” hearts supporting their feasibility in autologous cell transplantation. Clinical studies in animal models of MI have shown that cardio sphere injection into infarcted mouse and pig hearts preserves ventricular function, improves hemodynamic indices, produces less adverse remodel,and reduces infarct size (3).

2.4 Human Embryonic Stem Cells

Human embryonic stem cells grow and divide indefinitely while maintaining the potential to develop into derivatives of all three embryonic germ layers. Under appropriate culture conditions, a small fraction of (5–15%) spontaneously differentiate into CMs with structural and functional properties characteristic of endogenous CMs. Defined culture media have been developed to direct CM differentiation from human embryonic stem cell Coculture studies with mouse END2 cells have identified prostaglandin I2 as an inducer of CM differentiation.(6) Exposure to SB203580, a small-molecule inhibitor of p38MAPK, has also been observed to improve the efficiency of CM differentiation from human embryonic stem cell (23) and has implicated p38MAPK in the regulation of the ectoderm switch during early ESC differentiation. (24) Advances in understanding the genetic and epigenetic regulation of CM differentiation have also suggested potential new approaches to producing stem cell– derived CMs for therapy. The small, regulatory RNAs, microRNA and 133, are specifically expressed in the mouse heart, and their targeted deletion

or knockdown results in dysregulation of cardiac morphogenesis, electrical conduction, cell cycle, and cardiac hypertrophy Lentiviral induction of either miR-1 or miR-133 expression in enhanced early mesoderm differentiation and repressed development of endoderm and neuroectoderm. However, further differentiation revealed a predominant role for miR-1 in promoting the differentiation of or derived mesoderm
into cardiac and skeletal muscle cells. More recently, Wong et al. have shown that miR-125b similarly controls early CM specification through its effects on the pluripotent factors LIN28.

. Approaches to preparing embryonic stem cell- and induced pluripotent stem cell- derived cardiomyocytes (CMs) for tissue repair. Methods for directing differentiation of pluripotent stem cells to CMs have focused on chemical (e.g., 5-azacytidine, p38MAPK inhibitors, PGI2) and bio logical (e.g., activin A, bone morphogenetic protein, basic fibroblast growth factor, vascular endothelial growth factor, homolog 1) factors, genetic and epigenetic chromatin remodel manipulation, and mechanical factors (e.g., hydrodynamics, surface tension). In transplantation experiments, these approaches have been complemented by purification methods that take advantage of the biochemical properties of CMs density centrifugation, mitochondrial con tent), and selection strategies that rely on the expression of cardiac-specific genes (e.g., reporter lines, molecular beacons) and surface markers. determination by controlling protein dosage, epigenetic regulation through chromatin remodelhas been shown to control cell fate as well. Takeuchi et al. identified a minimal set of factors necessary to execute the cardiac transcriptional program.

Baf60c, a cardiac-enriched subunit of the like barrier-to-autointegration (BAF) chromatin remodel complex, in combination with cardiac transcription factors guanine-adenine-thymine-adenine (GATA) motif binding zinc finger transcription factor-4 (Gata4) and T-box transcription factor-5 (Tbx5), was able to induce cardiac differentiation in mouse embryos when ectopically expressed (22) Collectively, fluorescence-activated cell sorting or antibiotic selection of these lines has yielded 85–99% pure CMs or cardiac progenitors. Expressing cells derived from the ventricular MLC2 (MLC2v) transgenic line formed stable intracardiac cell grafts following transplantation. Injection of neomycin resistance-selected into the hind limb muscles of SCID mice resulted in no teratoma formation. Contractile forces in puromycin resistance-selected CMs were similar to those generated by rat neonatal ventricular CMs. Whereas isolation of derived CMs from these lines was based on positive selection, Anderson et al. implemented a negative select strategy to deplete undifferentiated, proliferating from cultures of derived CMs.(5)

2.5 Induced Pluripotent Stem Cells

The advent of induced pluripotent stem cell (iPSC) technology (17) offers a possible solution to immune rejection. This technology entails reprogramming terminally differentiated adult human fibroblasts to pluripotent stem cells through ectopic expression of four pluripotency factors: OCT4, SOX2, c-MYC, and KLF4. Reprogrammed cells exhibit many features characteristic of including morphology, cell surface. However, a recent study showed that isogenic iPSCs may still elicit an immune response.

2.6 Induced CM s

A recent study provides another promising approach to bypassing immune rejection. identified a minimal set of transcription factors to reprogram postnatal cardiac fibroblasts into functional CMs. (29) They showed that Gata4, myocyte enhancer factor-2c (Mef2c), and Tbx5 were sufficient for CM induction. Induced CMs expressed cardiac genes, exhibited calcium oscillations, and possessed action potentials resembling those of adult ventricular CMs. Some induced CMs reprogrammed fully to display spontaneous contractile activity. In vivo, cardiacfibroblasts transduced with Gata4, Mef2c, and Tbx5 transdifferentiated into CMs within 2 after injection into immunosuppressed mouse hearts.

3.1 Skeletal myoblasts

One of the first cell-based cardiac regeneration strategies was injection of autologous skeletal myoblasts into ischaemic myocardium. Myoblasts are resistant to ischaemia, can differentiate into myotubes in vivo (but not into cardiomyocytes and improve ventricular function in laboratory animal experiments. Human trials of myoblasts in heart failure are ongoing; however, some have been terminated because of lack of efficacy (13) and it is unlikely that skeletal myoblasts will be able to truly regenerate myocardium. Mouse skeletal muscle contains a population of non-satellite cells that can differentiate into spontaneously beating cells with cardiomyocyte features.

3.2 Bone-marrow-Derived cells

A subset of bone-marrow-derived hematopoietic cells were the first adult stem cells or progenitor cells reported to differentiate into cardio myocytes when transplanted into infarcted hearts of mice. The first evidence that adult bone-marrow-derived progenitor cells participate in the formation of cardiomyocytes in adult human hearts was based on reports of Y- chromosome-positive cardiomyocytes in female donor hearts transplanted in male recipients. (14) However, other studies in animals have not demonstrated differentiation of haematopoietic progenitor cells into cardiomyocytes or improvement in cardiac function.

Currently, no consensus exists on whether bone-marrow derived progenitor cells differentiate into cardiomyocytes in vivo.

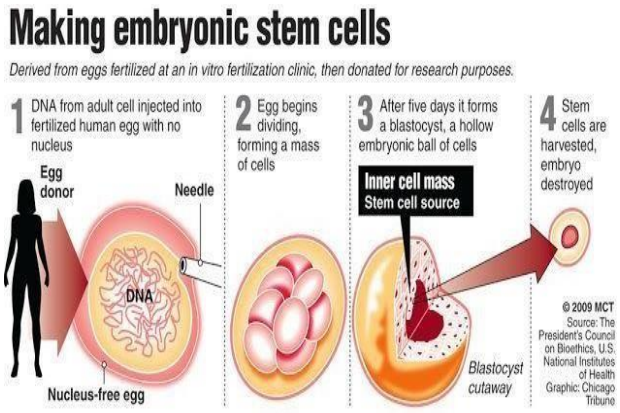

Figure 1

3.3 Embryonic stem cells

Embryonic stem (ES) cells are the prototypical stem cells. They unmistakably fulfil allrequirements of stem cells: clonality, self renewal and /Many cell types and mechanisms have been proposed for cardiac therapy. Stem cells and progenitor cells can be isolated from either autologous or allogeneic sources. Different types of stem cell and progenitor cell have been shown to improve cardiac function through variousmechanisms, including the formation of new myocytes, endothelial cells and vascular smooth muscle cells, as well as through paracrine effects.

3.4 Endogenous cardiac stem cells

Because allogeneic cells face immunological challenges that would probably require immunosuppression, the isolation of endogenous adult mammalian CSCs on the basis of cell- surface markers has generated great enthusiasm.(10) However, a definitive marker for CSCs has not yet been identified. Side-population cells, identified by their ability to exclude Hoechst dye, were first described in the bone marrow as being enriched in hematopoietic stem cells, but they are also found in other organs, including the heart.

4. Other related stem cells and CMs

4.1. Genes used to induce differentiation into CMs directly

Significant progress has been made in the indirect induction of CMs viatrans differentiation based on iPSC technology. In 2010, Srivastava et al. were the first to use a combination of GATA4, Mefc2 and Tbx5 (GMT) to transfect mouse fibroblasts, and they foundthat 20 percent of fibroblasts were reprogrammed into iCMs according to the expression of CM-specific proteins.

4.2 EPDCs: Heart tissue contains many components, including different types of heart cells (vascular smooth muscle cells, endothelial cells, and cardiac f ibroblasts), which also need to be modified and converted regularly to maintain a stable supply of myocardial tissue; these are referred to as EPDCs.(5) Additionally, after MI, activated EPDCs may form new myocardial cells to replace the lost myocardial cells. EPDCs thus simplify the regeneration of damaged myocardium and are active cells that provide a viable pathway for cardiac rehabilitation (14) However, the molecular mechanisms behind their activation and transition to mesenchymalcells remain unknown.

5 Cardiac stem cell-derived exosomes and microRNAs

Exosomes contain a large amount of microRNA and protein related to cellular structureand function, with unique biological characteristics and a subcellular structure [30]. Exosomeshave been documented to play a prominent role in acute and chronic ischaemia models and acute ischaemia-reperfusion injury models by significantly reducing infarction, reducing fibrosis and associated pathological remodelling, stimulating angiogenesis and modifying immune function, and preventing injury to the myocardium

introduction of miR-133, CM beating was observed on the 10th day after induction, while cells treated with GMT alone began to beat after approximately four weeks . In addition, scientists have confirmed that stem cell-derived exosomes have the following advantages:

- Stem cell-derived exosomes can be used to target cells with active molecules, such as mRNAs, miRNAs, and proteins. Simultaneously, these molecules can be changed through external means, such as source cell modulation.
- Similar to treatment with stem cells, treatment with only stem cell- derived exosomes can decrease the likelihood of immune rejection. Due to the complexity and low efficiency of exosome isolation and purification, the lack of the ability of exosomes to regenerate, and the limited half-life of exosomes, exosomes can provide only short-term benefits

6 Myocardial regeneration without stem cells

Current concepts of cell-based therapies are focused on the facilitation of endogenous repair processes by transplanted stem cells rather than through the actual regeneration of the lost cardi ac cells. (17) The observation of paracrine effects of stem cells, which have been shown to trigger angiogenesis, prevent apoptosis of myocardial cells, induce the proliferation of endogenous cardio myocytes and recruit resident CSCs, has stimulated an emerging concept of myocardial regeneration therapy. (21) In situ activation of paracrine signaling to initiate effective endogenous myocardial repair without stem cell transplantation would help avoid some major concerns associated with stem cell transplantation, such as delayed injection after acute injury for stem cell preparation, the high cost of the procedure, issues concerning the most effective route of delivery, and insufficient retention of the transplanted cells in damaged

tissue.

Future perspectives

In many studies, the number of differentiated and functionally integrated myocytes derived from transplanted stem cells is too small to explain the observed improvements in cardiac function. The past decade has improved our knowledge of stem cell biology and the development of the cardiovascular system. However, a more profound understanding of cardiac myogenesis will be required for the development of

advanced stem cell therapeutics to repair or regenerate damaged myocardium. As the barriers that prevent human cardiac regeneration are further defined, clinical trials should proceed with caution and with a paramount concern for patient safety.

Conclusion

Stem cell therapy is a novel and promising therapeutic modality for patients with significant cardiac dysfunction. Although many experimental studies and clinical trials have proven the feasibility, safety, and efficacy of cell-based cardiomyoplasty, the mechanisms underlying the regeneration of damaged cardiac tissues by stem cells are not fully understood. Since conventional drug therapy to surgical treatment and from stem cell transplantation to 3D cardiac printing, research related to cardiac regeneration therapy has produced constant breakthroughs in recent years. In addition, modern developments in cardiac regeneration therapy are also conducive to the development of current and successful forms of treatment for regeneration after heart failure. Significant breakthroughs have been made in stem cell researchfor cardiac regeneration.

Author contributions

All authors are contributed equally.

Financial support

None

Declaration of Competing Interest

The authors have no conflicts of interest to declare.

Acknowledgements

None

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