Cardiovascular Diseases: Recent Developments in Regenerative Medicine

Abstract

Advent of regenerative medicine has opened new therapeutic interventions for patients with cardiovascular diseases. The stem cell based cardiac repairing and regeneration along with improved vascularisation can improve diseased heart. Clinical studies over last decade have evaluated the cardiogenic potential of embryonic, induced pluripotent, cardiac, mesenchymal and bone marrow derived stem cells. The clinical studies have raised the hope of successful translation of regenerative cells from bench to bed side. Intrinsic factors guiding the stem cells to site of injury i.e. homing, transformation into cardiomyocytes, and angiogenesis have been assessed in recent years. However, complete understanding of mechanisms co-relating and regulating the process need to be explored. This review focuses on characteristics of stem cells under investigations, for clinical trials, analyzing safety, feasibility, efficacy and mechanism underling cardio protective and cardiac regenerative process. Further, the approaches involving scaffold based 3-dimensional cardiac generation will also be analysed.

Keywords: Mesenchymal stem cells; Cardiomyocytes; Cardiac regeneration; Embryonic stem cells; Pluripotent stem cells; ISSCR

Abbreviations: CSCs: Cardiac Stem Cells; BMMNCs: Bone Marrow Mononuclear Cells; ESCs: Embryonic Stem Cells; iPSCs: Induced Pluripotent Stem Cells; MSCs: Mesenchymal Stem Cells; bFGF: Basic Fibroblast Growth Factor; IL: Interleukin; TNF: Tumor Necrosis Factor; ISSCR: International Society for Stem Cell Research

The heart failure is one of leading cause of morbidity and mortality all over the world. More than 5 million patients are suffering from chronic heart failure post myocardial infarction caused due to ischemic heart disease [1]. The disease develops over a period of time due to loss of cardiomyocytes. The condition is further aggravated due to complications related to obesity, hypertension, diabetes, smoking and alcohol consumption. The currently available treatments regime include application of ACE (angiotensin converting enzymes) inhibitors, ARBs (angiotensin II receptor blockers) and aldosterone antagonists [2]. In selected patients cardiac resynchronization therapy and implantable defibrillators are also recommended [3]. Though, the treatment improves condition of patients symptomatically, no remarkable change in mortality or morbidity is observed. Heart transplant is not feasible due to unavailability of donors and possible immune rejection. New interventions, based on stem cell driven regeneration appear to be promising in current scenario. The cardiac regeneration can bring endogenous repair through formation of new cardiomyocytes and improved vascularisation.

The regenerative capacity of adult human myocardium was considered to be limited as myocardial cells are terminally differentiated. However, discovery of cardiac progenitor cells developed the possibility of heart tissue repair through cardiomyocytes generation. The process involves replacement of damaged myocardial cells with new one, derived from pluripotent cells. The major source for pluripotent cells are human embryonic (hESCs) and induced pluripotent stem cells (iPSC). The hESCs are considered to be promising candidate for cardiac cells development as their cardiogenic potential is established and further they can differentiate into multiligneage smooth muscle and endothelial cells, required in myocardial tissue. However, clinical use of hESCs and iPSCs still needs detail investigation to assess safety and efficacy. hESCs are derived from embryo which differs from parent in their genome. Similarly iPSCs also demonstrate genetic variability. The risk of immune rejection in such genetically variable cells is high. Both these cells type, if infused in undifferentiated state can lead to teratoma formation [4,5]. Another aspect which limits the application of hESCs is ethical issues associated with use of embryonic cells.

Bone Marrow Derived Stem Cells

Bone marrow is potential source of stem cells comprising of mixed population of cells mainly primary early stage committed cells, hematopoetic stem cells, endothelial progenitor cells and MSCs. Several studies have evaluated the functional myocardial activity by infusing bone marrow mononuclear cells (BMMNCs). In one major clinical trial, REPAIR, patients with acute myocardial infarction (AMI) were treated with bone marrow derived stem progenitor cells. 204 patients received intracoronary administration of autologus stem cells. After one year, significant reduction in occurrence of adverse events and improved vascular repair was observed. These beneficial effects were observed even after two years of follow up [6-9]. Similar, results were observed in different studies using administration of CD34+ cells in patients

Volume 3 Issue 2 - 2017

Anjum Mahmood1, Hiteshree Pandya1, Rajasekar Seetharaman1, Divyang Patel1, Anand S Srivastava2* 1GIOSTAR Research Pvt Ltd., India 2Global Institute of Stem Cell Therapy and Research, USA

*Corresponding author: Anand S Srivastava, Global Institute of Stem Cell Therapy and Research, 4370 La Jolla Village Drive San Diego, CA 92122, USA, Email: anand@giostar.com

Received: July 03, 2017 | Published: July 31, 2017

Abbreviations: CSCs: Cardiac Stem Cells; BMMNCs: Bone Marrow Mononuclear Cells; ESCs: Embryonic Stem Cells; iPSCs: Induced Pluripotent Stem Cells; MSCs: Mesenchymal Stem Cells; bFGF: Basic Fibroblast Growth Factor; IL: Interleukin; TNF: Tumor Necrosis Factor; ISSCR: International Society for Stem Cell Research
of angina and myocardial ischemia demonstrated improvement in frequency of angina and exercise tolerance [10,11]. However, despite of moderate success in bone marrow derived stem cells, some of the trials demonstrated little or no improvement after cell transplant. In a set of randomized trials, under category FOCUS-CCCTR and Late TIME trials, BMNNCs were infused to assess several parameters including myocardial perfusions, oxygen consumption and left ventricular function. The end result of trials concluded that cellular infusion did not improve oxygen consumption and left ventricular dysfunction [12-14].

Mesenchymal Stem Cells

Adult cells like mesenchymal stem cells (MSCs) are also capable of driving heart repair. MSCs are characterized by self renewal ability, low immunogenicity, no transplant rejection in host body and low tumorigenity. They lack major histo-compatibility complex II (MHC II) and B7 co-stimulatory molecule expression, so can easily escape the immune system and overcome host rejection. Though, MSCs lack the ability to differentiate into cardiomyocytes, they contribute to neo vascularization and cardiomyocyte protection [15]. Several studies have investigated the ability of MSCs in improving cardiac functions. In PRECISE trial, patients with ischemic cardiomyopathy were treated with adipose derived regenerative cells. Maximum oxygen consumption, ventricular function and exercise capacity was improved in treated group patients which suggested a reduction in inducible ischemia up to 18 months [16]. Some studies used allogenic source of MSCs as they are considered to be immunoprivileged and immunosuppressed [17,18]. A comparative study analysed two types of bone marrow transplants using allogenic and autologus source of cells. In this randomized phase 1/2 POSEIDON study, both types of cells demonstrated safety and potential to regenerate by reducing infarct size and ventricular remodelling [19]. In another study, Cardiopietic stem Cell therapy in heart failure (C-CURE), bone marrow derived MSCs, treated with a particular cardiogenic cocktail, were used for infusion in patients with heart failure. The safety and feasibility was observed, with indications of benefit. Though some concerns were raised about the methodology of trial, the reply by investigators was submitted and published in same journal. Meanwhile, Cardio3biosciences, which conducted C-CURE trial, is working on phase III trial of study [20,21].

Cardiac Stem Cells

They are heterogeneous group of cells, are categorized as cardiac stem cells (CSCs). They are heterogeneous group of cells residing in specific heart areas as atria or pericardium and are characterized by expression of c-kit+ surface marker [22,23]. Several trials used CSCs in their clinical study. Stem Cell Infusion in Patients with Ischemic Cardiomyopathy (SCIPIO) trial used c-kit+ CSCs in patients with heart failure due to IHD in phase 1 trial. The results were encouraging as it suggested intracorony infusion of CSCs led to improved LV systolic function and reduced infarct size. An unprecedent increase in viable myocardium was reported due to therapeutic regeneration [24]. At almost same time, Makkar et. al. published a report demonstrating the use of cardiopietic derived cells (CDCs) in patients with left ventricular dysfunction in a randomized phase 1 trial of cardiopietic derived cells for heart regeneration after myocardial infarction (CADUCEUS). The results demonstrated that infusion was safe and an increase in viable myocardial tissue was observed. The scar size reduction was claimed to be 3-5 times better than in case of bone marrow mononuclear cells used in other studies [25].

The clinical assessment of stem cell based intervention demonstrated feasibility and safety of transplant; however, the efficacy remained an issue. The variable efficacy of transplants can be understood on basis of mechanism governing mode of action of administered cells.

Mechanism Underlying Myocardial Activity Conferred by Stem Cell Transplants

Cardiogenic cells including ESCs and iPSCs stimulate heart repair by stimulating differentiation to cardiomyocytes. However, exact mechanism regulating the process is not completely understood. Paracrine signalling has been attributed main driving force behind cardiac repair. The mechanism can be categorized into cardio protection, angiogenesis, myogenesis and endogenous repair. The cardio protection is conferred by secretory anti-apoptotic factors. Once inside body, MSCs inhibit activation of transcription factor NF-κB in B cells, which in turn attenuates secretion of pro-inflammatory, factors TNF-α and IL-6, and promotes anti-inflammatory cytokine IL-10. TNF-α and IL-6 are toxic to cardiomyocyte activity and cause reduced contractile activity and induce apoptosis [26]. MSCs regulate immune response and induce IL-10 secretion through monocytes and macrophages which in turn inhibits NF-κB nuclear factor. Along with cardioprotection, MSCs secrete angiogenic vascular endothelial growth factor (VEGF) and arteriogenic basic fibroblast growth factor (bFGF). VEGF increases capillary wall permeability, induces cell proliferation, migration and vascularisation. On other hand, bFGF promotes smooth muscle formation as part of angiogenesis [27,28].

Myocardial infarction leads to accumulation of collagen resulting into fibrosis. Under fibrotic environment expression of many genes, growth factors and cytokine is downregulated resulting into inhibition of endogenous cardiac repair [29]. Under such environment, MSCs transplantation brings about modulation of matrix by metalloproteinase resulting into matrix degradation activity. MSCs control fibroblast activity by down regulating synthesis of type I and type III collagen synthesis and finally inhibit ventricular remodelling. Along with matrix regulation, MSCs cause endogenous cardiac repair through stimulation of, c-kit+ cardiac stem cells and cardiomyocyte cell division [30,31].

Researchers have proposed another way through which MSCs may impart cardiac repairing function. The MSCs along with other factors, secrete exosomes which are vesicles containing biological molecules primarily proteins, mRNA, microRNA and lipid [32]. Exosomes play vital role in cell-cell interaction and mediating bidirectional exchange of material. These exosomes induce angiogenesis in endothelial cells by direct transfer of mRNA. Timmers L et al. [33] demonstrated that media conditioned with hMSC reduce infarct size by 59% in animal model of myocardial ischemia [33].
The safety, feasibility and efficacy of stem cell transplant in cardiovascular diseases have been studied in numerous trials using wide range of stem cells. However, each approach is associated with various benefits and limitations. Though, ESCs and iPSCs are potentially capable of generating new cardiomyocytes, infusion of undifferentiated cell may lead to teratomas formation. Further, use of ESCs involves ethical concerns. Adult stem cells like CSCs and MSCs appear to be potentially more feasible for clinical transplants. CSCs, directly or indirectly through MSCs, can be induced for endogenous cardiac repair. Additionally, they are not associated with tumor formation, which is major advantage. MSCs exerts cardio-protective and regenerative effect through several mechanisms including secretion of growth factors VEGF, bFGF, metalloproteinases, exosomes and stimulation of endogenous c-kit+ CSCs. Though, MSCs themselves lack the ability to differentiate into cardiomyocytes, they provide beneficiary effect through paracrine signals.

Tissue Engineering

Along with cell based approaches for damaged cardiac repair, researchers have explored the concept of in-vitro 3 dimensional generation of complete heart. Emerging trends in tissue engineering indicate towards possible generation of cardiac structures. The methodology involves re-population of cardiomyocytes and endothelial cells around a natural (extracellular) or synthetic matrix based scaffold. Reprogrammed iPSCs are primary source of cells, incorporated in engineered construct. The selection of scaffold depends on elasticity, biocompatibility and biodegradability of material. Further, the structure must be interconnected, appropriately porous and supportive for cell proliferation and differentiation of stem cells. The extracellular matrix protein (ECMP) based biomaterials are natural option for scaffolds developments in cardiac engineering and regeneration as they are bio-compatible. However, the decellularized matrices are superior to ECMP based, as later one does not mimic the complexity and structure of native tissue. The decellularized matrices are obtained through detergent treatment of intact cardiac tissue. The process retains intact vasculature and complex 3D arrangement of collagens, elastin and glycosaminoglycan[34]. The decellularized scaffold was successfully tested initially in rat, by recellularization of neonatal cardiomyocytes [35]. However, human organ generation using decellularized scaffolds is limited due to unavailability of intact hearts. Due to this animal based heart structures closely resembling to humans are under investigation. Synthetic polymers which have been investigated till now are based on poly (lactic acid) (PLA), poly(ethylene glycol) (PEG), poly(caprolactone) (PCL), poly(l-lactide-co-caprolactone) (PLCL), poly(glycerol sebacate) (PGS), and polyurethane (PU) [36,37].

Future Directions

Clinical trials conducted over last few years have generated substantial data on implications of regenerative medicine on cardiovascular disease. Most of data are based on results of early phase I and phase II studies. Contradictory results in several studies have raised concern over methods adopted during trial design. To deal with such issues and bring transparency in clinical trials procedures, International Society for Stem Cell Research (ISSCR) has issued revised guidelines to be followed. These guidelines are aimed to encourage best practices in translational and clinical research. Under current scenario, in many cases, where conventional treatment fails to provide prolonged relief to cardiovascular patients, new interventions are required which can provide less invasive, sustained and cost effective benefits. Stem cell based repair or transplant of in-vitro developed cardiac structure in cardiovascular diseases open a wide array of opportunities to healthcare system where scientists, clinicians and developers can contribute keeping ethical values in practice.

References

1. Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, et al. (2012) Heart disease and stroke statistics - 2012 update: a report from the American Heart Association. Circulation 125(1): e2-e220.

2. Montecucco F, Mach FS (2009) ACE inhibitors and ARBs in cardiovascular disease. Best Pract Res Clin Endocrinol Metab 23(3): 389-400.

3. Pun PH, Sheng S, Sanders G, DeVore AD, Friedman D, et al. (2016) Prescription of Guideline-Recommended Implantable Cardioverter Defibrillator and Cardiac Resynchronization Therapy Among Patients Hospitalized With Heart Failure and Varying Degrees of Renal Function. Am J Cardiol 119(6): 886-892.

4. Murata M, Tohyama S, Fukuda K (2010) Impacts of recent advances in cardiovascular regenerative medicine on clinical therapies, and drug discovery. Pharmacol Ther 126(2): 109-118.

5. Chambers I, Smith A (2004) Self renewal of tentacarcinoma and embryonic stem cells. Oncogene 23(43): 7150-7160.

6. Schächinger V, Erbs S, Elsässer A, Haberbosch W, Hambrecht R, et al. (2006) Improved clinical outcome after intra coronary administration of bone-marrow-derived progenitor cells in acute myocardial infarction: final 1-year results of the REPAIR-AMI trial. Eur Heart J 27(23): 2775-2783.

7. Erbs S, Linke A, Schächinger V, Assmus B, Thiele H, et al. (2007) Restoration of microvascular function in the infarct-related artery by intra coronary transplantation of bone marrow progenitor cells in patients with acute myocardial infarction: the Doppler Substudy of the Reinfusion of Enriched Progenitor Cells and Infarct Remodeling in Acute Myocardial Infarction (REPAIR-AMI) trial. Circulation 116(4): 366-374.

8. Dill T, Schächinger V, Rolf A, Mollmann S, Thiele H, et al. (2009) Intra coronary administration of bone marrow-derived progenitor cells improves left ventricular function in patients at risk for adverse remodeling after acute ST-segment elevation myocardial infarction: results of the Reinfusion of Enriched Progenitor Cells And Infarct Remodeling in Acute Myocardial Infarction study (REPAIR-AMI) cardiac magnetic resonance imaging sub-study. Am Heart J 157(3): 541-547.

9. Assmus B, Rolf A, Erbs S, Elsässer A, Haberbosch W, et al. (2010) Clinical outcome 2 years after intra coronary administration of bone marrow-derived progenitor cells in acute myocardial infarction. Circ Heart Fail 3(1): 89-96.

10. Perin EC, Willerson JT (2011) CD34+ autologous human stem cells in treating refractory angina. Circulation Research 109(4): 351-352.

11. Povsic TJ, Junge C, Nada A, Schatz RA, Harrington RA, et al. (2013) A phase 3, randomized, double-blinded, active-controlled, unblinded standard of care study assessing the efficacy and safety of intramyocardial autologous CD34+ cell administration in patients with refractory angina: design of the renew study. American Heart Journal 165(6): 854-861.
12. Perin EC, Willerson JT, Pepine CJ, Henry TD, Ellis SG, et al. (2012) Cardiovascular Cell Therapy Research Network (CCTRN). Effect of transendocardial delivery of autologous bone marrow mononuclear cells on functional capacity, left ventricular function, and perfusion in chronic heart failure: the FOCUS-CCTRN trial. JAMA 307(16): 1717-1726.

13. Traverse JH, Henry TD, Pepine CJ, Willerson JT3, Ellis SG (2014) One-Year Follow-up of Intracoronary Stem Cell Delivery on Left- Ventricular Function Following ST-Elevation Myocardial Infarction. JAMA 311(3): 301-302.

14. Traverse JH, Henry TD, Ellis SG, Pepine CJ, Willerson JT, et al. (2011) Cardiovascular Cell Therapy Research Network. Effect of intracoronary delivery of autologous bone marrow mononuclear cells 2 to 3 weeks following acute myocardial infarction on left ventricular function: the Late TIME randomized trial. JAMA 306(19): 2110-2119.

15. Kuraitis D, Ruel M, Suurnen HE. (2011) Mesenchymal stem cells for cardiovascular regeneration. Cardiovasc Drugs Ther 25(4): 349-362.

16. Perin EC, Sanz-Ruiz R, Sánchez PL, Lasso J, Pérez-Cano R, et al. (2014) Adipose-derived regenerative cells in patients with ischemic cardiomyopathy: The PREGISE Trial. Am Heart J 68(1): 88-95.

17. Liang J, Zhang H, Hua B, Wang H, Lu L, et al. (2010) Allogenic mesenchymal stem cells transplantation in refractory systemic lupus erythematosus: a pilot clinical study. Ann Rheum Dis 69(8): 1423-1429.

18. Quevedo HC, Hatzistergos KE, Oskouei BN, Feigenbaum GS, Rodriguez JE, et al. (2009) Allogeneic mesenchymal stem cells restore cardiac function in chronic ischemic cardiomyopathy via trilineage differentiating capacity. Proc Natl Acad Sci USA 106(33): 14022-14027.

19. Hare JM, Fishman JE, Gerstenblith G, DiFede Velazquez DL, Zambrano JP, Sunchon VY, et al. (2012) Comparison of allogeneic vs autologous bone marrow-derived mesenchymal stem cells delivered by transendocardial injection in patients with ischemic cardiomyopathy: the POSEIDON randomized trial. JAMA 308(22): 2369-2379.

20. Bartunek J, Behfar A, Dolutahadi D, Vanderheyden M, Ostoje M, et al. (2013) Cardiopoietic stem cell therapy in heart failure: the C-CURE (Cardiopoietic stem Cell Therapy in heart failURE) multicenter randomized trial with lineage-specific biologics. J Am Coll Cardiol 61(23): 2293-2308.

21. Abbott A (2014) Doubts over heart stem-cell therapy. Nature 509(7498): 15-16.

22. Beltrami AP, Urbanek K, Kajstura J, Yan SM, Finato N, et al. (2001) Evidence that human cardiac myocytes divide after myocardial infarction. N Engl J Med 344: 1750-1757.

23. Messina E, De Angelis L, Frati G, Morrone S, Chimenti S, et al. (2004) Isolation and expansion of adult cardiac stem cells from human and murine heart. Circulation Res 95: 911-921.

24. BoBi R, Chugh AR, D’Amario D, Loughran JH, Stoddard MF, et al. (2011) Cardiac stem cells in patients with ischaemic cardiomyopathy (SClPIO): initial results of a randomised phase 1 trial. Lancet 378(9806): 1947-1957.

25. Makkar RR, Smith RR, Cheng K, Malleras K, Thomson LE, et al. (2012) Intracoronary cardiosphere-derived cells for heart regeneration after myocardial infarction (CADUCEUS): a prospective, randomised phase 1 trial. Lancet 379(9819): 895-904.

26. Du Y, Zhou SH, Zhou T, Su H, Pan HW, et al. (2008) Immuno-inflammatory regulation effect of mesenchymal stem cell transplantation in a rat model of myocardial infarction. Cytotherapy 10(5): 469-478.

27. Testa U, Pannitteri G, Condorelli GL (2008) Vascular endothelial growth factors in cardiovascular medicine. Journal of Cardiovascular Medicine 9(12): 1190-1221.

28. Tang YL, Zhao Q, Xin Y, Shu L, Cheng L, et al. (2005) Paracrine action enhances the effects of autologous mesenchymal stem cell transplantation on vascular regeneration in rat model of myocardial infarction. Annals of Thoracic Surgery 80(1): 229-237.

29. Kinnaird T, Stabile Z, Burnett SM, Shou M, Lee CW, et al. (2004) Local delivery of marrow-derived stromal cells augments collateral perfusion through paracrine mechanisms. Circulation 109(12): 1543-1549.

30. Ohnishi S, Sumiyoshi H, Kitamura S, Nagaya N (2007) Mesenchymal stem cells attenuate cardiac fibroblast proliferation and collagen synthesis through paracrine actions. FEBS Letters 581(21): 3961-3966.

31. Karantalis V, Hare J (2015) Use of mesenchymal stem cells for therapy of cardiac disease. Circulation. Res 116(8): 1413-1430.

32. Baglio SR, Pegtel M, Baldin N (2012) Mesenchymal stem cell secreted vesicles provide novel opportunities in (stem) cell-free therapy. Front Physiol 3: 35.

33. Timmers L, Lim SK, Arslan F, Armstrong JS, Hoefer IE, et al. (2008) Reduction of myocardial infarct size by human mesenchymal stem cell conditioned medium. Stem Cell Research 1(2): 129-137.

34. DeQuach JA, Mezzano V, Miglani A, Lange S, Keller GM, et al. (2010) Simple and high yielding method for preparing tissue specific cell conditioned medium. Stem Cell Research 1(2): 129-137.

35. Taylor DA, Parikh RB, Sampao LC (2017) Bioengineering Hearts: Simple yet Complex. Curr Stem Cell Rep 3(1): 35-44.

36. Boffito M, Sartori S, Ciardelli G (2014) Polymeric scaffolds for cardiac tissue engineering: requirements and fabrication technologies. Polym Int 63(1): 2-11.

37. Ravichandran R, Venugopal JR, Sundararajan S, Mukherjee S, Sridhar R, et al. (2012) Minimally invasive injectable short nanofibers of poly(glycerol sebacate) for cardiac tissue engineering. Nanotechnology 23(38): 385102.