AZJCVS
AZerbaijan Journal of CardioVascular Surgery

AZJCVS 2021;2(2):63-7
DOI: 10.30546/azjcvs.2021.2.2.38

Review Article

Nigar Kazimzade

Department of Cardiovascular Surgery, Central Clinical Hospital, Baku, Azerbaijan

Received: 27 January, 2021
Accepted: 29 June, 2021
Published: 05 November, 2021

Corresponding Author: Nigar Kazimzade, Department of Cardiovascular Surgery, Central Clinical Hospital, Baku, Azerbaijan
Email: nigar-kazimzade@mail.ru

CITATION
Kazimzade N, Stem cell treatment perspectives for cardiovascular diseases. AZJCVS. 2021;1(2):63-7. DOI: 10.30546/azjcvs.2021.2.2.38

Stem cell treatment perspectives for cardiovascular diseases

Abstract
Ischemic cardiomyopathy is becoming a leading cause of morbidity and mortality in the whole world. Ischemic injury to the heart muscle often results in irreversible loss of myocardial tissue. At the latest stage the treatment of cardiac failure is the heart transplantation. But wide prevalence of heart failure coupled with lack of appropriate donors, makes the transplantation a non-sustainable solution for organ failure treatment . Thus, the insufficiency of current treatment method for cardiovascular diseases makes it necessary to explore and develop safe and effective alternatives. In order to repair and regenerate functional tissues or organs, researchers have focused on regenerative medicine. Recent developments in stem cell therapy provide new hopes in treatment of diseases that yet cannot be treated. There are no doubts that in the near future stem cells therapy will prove effective for cardiovascular diseases.

Keywords: Ischemic cardiomyopathy, stem cells, regenerative therapy

INTRODUCTION

Ischemic diseases had become a leading cause of death with social development and improvement of life standards. According to WHO statistics each year 17.9 million people die due to cardiovascular diseases, which is 31% of total mortality. 85% of this data account for myocardial infarction and brain stroke (1). Just in the USA 1 million people get myocardial infarction every year, with vast majority of them resulting in heart failure. Great number of patients, along with expensive treatment, makes cardiovascular diseases a huge economic burden (2).

There are different types of treatment of ischemic heart diseases and its complications in modern medicine, that already had become a standard. Though cardiac resynchronization, coronary angioplasty, coronary by-pass surgery, use of VAD (ventricular assist devices) and some medications are available for treatment. Most of them are palliative purposes as they only improve the quality of life of a patient, not being able to stop the progress of the disease itself. Although major achievements in the treatment of myocardial infraction are made in surgery, surgical intervention itself is limited to procedures on major vessels (3). On the other hand, microangiopathy, microcirculation failure, diffuse coronary disease, multiple interventions and surgeries, arterio-venous conduit insufficiency make the ischemia persistent as a main reason for inoperable condition. Continuing ischemia causes the death of cardiomyocytes, which, in turn, gets substituted with fibroblasts, resulting in cardiac muscle being substituted with fibrous, non-contracting tissue. This staged process called cardiac remodeling, causing pathologic dilatation and cardiac failure (4). At the latest stage the treatment of cardiac failure is the heart transplantation. Wide prevalence of heart failure coupled with lack of appropriate donors, makes the transplantation a non-sustainable solution for organ failure treatment (5). Thus, the insufficiency of current treatment method for cardiovascular diseases makes it necessary to explore and develop safe and effective alternatives.

Until recently the heart was considered a terminal stage differentiated organ with no regeneration capacity. However,

it was recently confirmed that depending on age the annual regeneration rate of cardiomyocytes is a 0.4-1%. It should be mentioned that the number of myocytes lost during infarction is about a billion, which is about 25% of the left ventricle (the number of cardiomyocytes in the left ventricle is 2-4 billion) (6). The ability of 1% of cardiomyocytes to renew itself doesn't create an opportunity to fight against such serious lesions as large-scale myocardial infarction. The apoptosis and necrosis of cardiomyocytes due to ischemia violate the geometry of left ventricle giving a start to ventricle remodeling, hypertrophy and substitution of myocardia with scar tissue as a result of activation of fibroblasts (7). These changes are peculiar to cardiomyopathy.

Classification of stem cells

Real stem cells have special, determinant features or criteria:

1. Proliferation (self-renewal, unlimited duplication without differentiation)
2. Differentiation (get transformed into different types of cells) (8). Stem cells are mostly classified based on ability to differentiate and on origin.

Based on differentiation ability stem cells are divided in to totipotent, pluripotent, multipotent and unipotent types. Totipotency is the feature of cells that can differentiate in to any type of embryonal and extra-embryonal cells. It is possible to get an entire organism from cells of an embryo that appears from fertilized cell. Pluripotent cell are more specialized, maintain functions of renewal and differentiation, can give origin to the cells of all three layers (ecto-, meso- and endodermal) of an embryo, however they do not have an ability to form an entire organism (for example, embryonal cells). Multipotent cells are even more specialized, have already differentiated in to ecto-, meso- and endodermal cells and can give an origin to most of tissue cells. They are referred to hemopoietic and mesenchymal cells. Unipotent cells already lost the feature of renewal, however, can give and origin to any type of cells.

Based on origin stem cell are divided in to 2 groups

Embryonal and tissue originated (somatic) cell (9). Somatic cell, in turn, are divided in to cells originating from fetal (placenta, amniotic fluid, umbilical cord) and matured different tissue (bone marrow, skin, peripheric blood, heart, etc.) cells (10). Recently two more sub-groups of tissue originated cells are explored: induced pluripotent cells and induced tissue specific stem (11).

In modern medicine two types of stem cells are used for cardiac regeneration: multipotent-adult (matured) or somatic stem cells and pluripotent (embryogenic) or induced pluripotent (iPSC) cells. From the perspective of a potential therapeutic effect the first two groups have their own advantages and shortcomings (12).

Embryonal cells. Embryonal cells appear from 8-cell stage (around 5-7 days since conception) as next one after the germ. ESC, after extraction from internal cell of blastocyst, are placed under special conditions to multiply through endless division. As the separation of undifferentiated cell is very difficult, the formation of teratoma is reported. Thus, embryonal cell are prone to tumor formation. This imposes limitation on the use of this group of cell (13,14).

Induced pluripotent cells (iPSC)

During 2006-2009 successful reprograming of somatic cells, similar to stem cells was reported by 3 independent groups. For the first time the Nobel price laureate Yamanaka et.al. had successfully reprogramed fibroblasts of mice. Later iPSC was obtained from human skin fibroblasts (15). iPS cells are those originating from somatic cells with the expression of embryonal genes or genes called "Yamanaka's factor" (Okt4/3, c-Myc, Klf4, etc.). The following are the advantages of embryonal and induced pluripotent cells: pluripotency (ability to proliferate and differentiate unlimited, give origin to any type of cells), in vitro effective expansion, possibility to create a cells bank, as well as autogenic cells in iPSC sample. However, regardless of these, the production of the final therapeutic product requires a lot of time, as a result, micro-RNA gets out of control leading to genetic anomalies, the risk of teratoma developing from final cells, on top of that use of allogenic embryonal cell induces immune system reaction which may lead to acute complications limits the use of such cells and requires additional research in future (12).

The primary objective of somatic cell reprograming, and production of iPSC is to release somatic cells from own features and bring them back to the stage of embryonal cells. Though Yamanaka group's first experiments proved this, later studies showed iPSC preserving donor cells genetic template. It is important to take that into account during clinical studies and organ remodeling (16). On the other hand, unlike ESC, as iPSC production doesn't require destruction of embryo, not ethic issue emerges. However, some other ethic issues started to appear with regards to iPSC. One speaks here about human embryo and, even more important, human-animal chimeras appearing as a result of genetic engineering. Nevertheless, the progress in stem cell technology pushes scientists towards using iPSC human heart models to conduct basic research (17).

Mature stem cells

The history of mature stem cells start with the discovery of hemopoietic stem cells in a bone marrow back in 1909 (18). Mature or somatic cells, being the formation of multipotent stem and progenitor cells, can be obtained from different vascularized tissues (bone marrow, skeletal muscles, adipose tissue, lungs, heart). Most frequently used cells are: mononuclear cells from bone marrow, hemopoietic stem cells, endothelial progenitor cells, cardiac and mesenchymal stem cells (19). The primary function and duties of these cells is to ensure mature tissue homeostasis, to a limited extend, the tissue regeneration. However these cells have some disadvantages: they are very few in number in mature tissues, have limited ability to differentiate, it is difficult to obtain them in a number sufficient for therapeutic

purposes, immunogenicity and arrythmia pertinent to stem cell transplantation. In terms of cardiac regeneration, different types of stem cells had been used over the last decade, researches were performed, mechanism of action and efficiency was studied (20).

Potential therapeutic features of stem cells

There are two different, yet complementing each over at the same time objectives of the stem cell therapy:

1. The direct substitution of damaged myocardia with contractile cardiomyocytes;
2. Influencing endogenous rehabilitation processes like angiogenesis, inflammation, apoptosis and fibrosis by means of paracrine (local cell-to-cell) effects. Lets review both of them individually (21).

1) The direct cell or tissue substitution is the most desirable strategy in the field of myocardial muscle and function rehabilitation. Direct mechanism of action entails the substitution of necrotized cardiomyocytes with new functional cardiomyocytes and vascularized cells through proliferation and subsequent differentiation of stem cells (22). Rehabilitation of cardiac muscle is the only effective strategy against irreversible fibrosis and remodeling due to ischemia. However, in modern terms, the substitution therapy is still inaccessible. Regardless to first promising attempts, it has become apparent that non-cardiac cells from bone marrow or cells obtained from mature cardiac tissue later become ineffective or have no cardiomyogenic effect (23,24). Such cells mostly perform through non-contractile mechanisms (25,26). In contrary, pluripotent cells (ESC, iPSC) had manifested clear muscle rehabilitation potential during pre-clinical studies. However, muscle rehabilitation by itself has some questions yet to be answered: new myocardia can be arythmogenic or may require long-term immune suppressive strategies for successful cell implantation (21).

2) The second mechanism is called non-contractile or paracrine. An indirect action of stem cell on to the heart and vascular network is, reportedly, mediated by wide-range mediators, cytokines, chemokines, and growth factor production or release. The peculiarities of such mediators depend on implanted stem cells and the surrounding tissues environment of a recipient. A number of processes are related to paracrine effects:

1. Activation and proliferation of endogenic cardiac progenitor cells,
2. Activation of neovascularization through mobilization of different chemokines and proangiogenic factors, endogenic endothelial and progenitor cells,
3. Inhibition of apoptosis and myocyte hypertrophy,
4. Suppression of inflammation and immune regulation,
5. Remodeling of extra-cellular matrix, control over collagen synthesis and fibrosis,
6. Positive impact on myocardial metabolism and electrophysiology (21).

Currently researchers are focused on exocrine function of stem cells. Regenerative medicine had discovered extracellular vesicle (particles) for about 40 years now, however, only recently the role of these particles in angiogenesis and cell-to-cell communication became known. There are 3 different types of extracellular vesicles: exosomes, microvesicles and apoptotic bodies. Based on the content there are divided into protein, lipid nucleic acid carriers. Clinical practice mostly employs somatic multipotent cells for real regeneration of cardiomyocytes, and since the low level of survival and differentiation potential in the ischemic zone became known the attention shifted towards paracrine effect of transplanted stem cells (4).

Stem cells delivery methods

Currently these methods include transvascular and direct left ventricle (intramyocardial) delivery methods. Transvascular, in turn, include intracoronary, intravenous methods and stem cell mobilization. The most widespread are the following.

Intracoronary is the infusion of stem cells into coronary artery during the short-term balloon occlusion with central canal. Thus, temporary suspension of coronary flow prevents the dispersion of cells and provides for sufficient time for cells to migrate (extra-vasal) into myocardia itself (22). Distribution of cells into the zone of infarction, relatively easy and minimal invasive method, no need for additional equipment and extra expenditure, accessibility are used to describe positive aspects of this method yet there are some shortcomings as well: possibility of microcirculation occlusion with big cells, impossibility of cell delivery in the basin of completely occluded vessel.

Direct left ventricle (intramyocardial) infusion

Stem cell intramyocardial infusion is used as an alternative when trans-vascular method is not possible due to coronary artery occlusion or weak concentration, centralization signals. Preclinical studies showed that compare to intracoronary method, intramyocardial infusion provides for much higher level of retention of stem cells (26). However, though infusion creates some isle of stem cells, weak blood supply in the ischemic or scarry area compromises survival conditions, these isles can violate the architectonics of the myocardia and transform in to potential arrythmia site. Direct infusion is an advantage for use of big size cells. It should be noted that injection into a softened and weakened myocardia may be technically a challenge, resulting in perforation.

In general, there are trans-epicardial and trans-endocardial ways of injection. Trans-epicardial method can be employed as an extra procedure during coronary surgery under the visual control. Infusion into scarry zone of myocardia or new infarction zones allows for direct visual control, however, coupling with coronary by-pass prevents from objective assessment of the treatment outcomes (27).

Trans-endocardial infusion is about delivering stem cells, using a special catheter, on to the internal surface of left ventricle through aortal valve. A special 3D fluoroscopic catheter system provides for myocardial mapping, fibrosis, hibernation, contractile dysfunction, living tissue differentiation and delivery of stem cells into targeted area. However, cell isles at the injection spot may cause the death of cells due to inadequate blood supply. Along with factors, the way of cell delivery is one of important once, and choice depends, proper evaluation, doctor's experience and approach.

Stem cell treatment outcomes

Some researches show that stem cells (mostly bone marrow) are safe and successful in ischemic cardiopathy treatment. However, outcomes of other researches are still disputable. Wang's group metanalysis in 2019, covering 2004-2017, had reviewed 20 perspective randomized – controlled studies from among of 887 that met the requirements of metanalisys. These studies covered 1418 patients in total, of which, 705 had bone marrow stem cell implantation, the other 713 were in control group. Patients were within wide age range (30 to 80 years), and 71% of them were male. To assess the left ventricle performance LVEF, LVESV, LVEDV, 6-minute walking distance, NYHA functional indicators were used. At the same time, quality of life (MİHFQ score), MACE (major adverse cardiac events), rehospitalization rate and mortality for all causes were taken into account as treatment outcome. Echocardiograpy, MRI and PET examination were performed. Follow-up period was at least 1 month (3,6,12 months and more). According to the results of metanalysis in all patients with BMC transplantation LVEF, LVESV, 6-minute walking distance, NYHA functional class parameters, quality of life and mortality for all causes had significantly improved. LVEDV, MACE and rehospitalization manifested significant difference. This mostly indicates that BMC group had safe and appropriate therapy. In terms of research peculiarities, intra-coronary and intra-myocardial infusion of cells and the dose off cells were considered. When the number of implanted cells was 108 the outcomes were better than that of for patients with smaller dose. In terms of injection, intra-coronary method yielded in faster (already in 3 months), whereas intra-myocardial outcomes are observed 6 months later. Yet, while comparing 6 months' outcomes among both groups intra-myocardial groups shows better LVEF (28).

So, regardless of 15-20 years of experiences of using stem cells for the therapy of cardiovascular diseases, the subject is still at primary level. Although first steps were promising, the limited scale of studies and disappointed expectation created a certain degree of pessimism. However, failure is natural for new technologies, yet may yield in success. At the same time, safety of the therapy is of importance. There are no doubts that in a near future stem cell therapy will prove effective for cardiovascular diseases. Millions of heart patients all over the world are waiting this method of alternative technology, which will improve the quality of life and life expectancy (29).

Conflict of Interests: The authors declare that they have no competing interest.

Financial Disclosure: There are no financial supports.

Data Availability Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Association: This study is not associated with any thesis or dissertation work.

REFERENCES

1. who.int/health –topics/cardiovascular diseases. June 2021
2. Xianyun W, Jun Z, Fan Z, Jet ol. The clinical status of stem cell therapy for Ischemic Cardiomyopathy. Stem Cells Int 2015;2015:135023.
3. Mason D, Chen Y, Krishnan H, Sant S. Cardiac gene therapy: Recent advances and future direction. J Controlled Release. 2015;215;101-11.
4. Xiaowei B, Kui M, Cuiping Z, Xiaobing F. Therapeutic angiogenesis using stem cell-derived ectracellular vesicles:an emerging approach for treatment of ischemic disease. Stem Cell Res Ther. 2019:10;158.
5. Rosalinda M, Linda WL, Seam MD, Felix BA. Position paper of European Society of Cardiology working group cellular biology of the heart: cell-based therapies for myocardial repair and regeneration in ischemic heart disease and heart failure. Eur Heart J. 2016;37:1789-98.
6. Chen CH, Sereti KI, Wu BM, Ardehali R. Translational aspects of cardiac cell therapy. J Cell Molecular Med. 2015;19;1757-72.
7. Rajabzadeh N, Fathi E, Farahzadi R. Stem Cell Based Regenerative Medicine. Stem Cell Investigation 2019. doi:10.21037/sci2019.06.04
8. Edward H.Nteqe, Hiroshi Sunami, Yusuke Shimizy. Advances in regenerative medicine: a review of the literature and future directions. Regenerative therapy 14(2020) 136-53.
9. Ullah İ, Subbarao RB, Rho GJ. Human Mesenchymal Stem Cells - current trends and future prospective. Biosci Rep. 2015;35:00191.
10. Klopsch C. Skorska A, Ludwig M, et al. Cardiac Mesenchymal Stem Cells proliferate early in the ischemic heart. Eur Surg Res. 2017:58:341-53.
11. Zaehres H, Scholer HR. Induced Pluripotency: from mouse to human. Cell. 2007;131:834-5.
12. Lemcke H, Voronina N, Steinhoff G, David R. Recent progress in stem cell modification for cardiac regeneration.

Stem Cell Int. 2018;2018:1909346.

13. Ben David U, Benvenisty N. The tumorigenicity of human embrionic and induced pluripotent stem cell. Nat Rev Cancer. 2011;11;268-7
14. Valarevic V, Markovic BS, Gazdic M, et al. Ethical and safety issues of stem cell-based therapy. Int J Med Sci 2018;15:36.
15. Yu J, Vodyanik MA, Smuga Otto K, et al. Induced pluripotent stem cell derived from human somatic cells. Science. 2007;318:1917-20.
16. Maherali N, Sridharan R, Xie W, et al. Directly reprogrammed fibroblasts show epigenetic remodeling and widespread tissue contribution. Cell Stem Cell. 2007:1;55-70.
17. Samak M, Hinkel R. Stem cells in cardiovascular medicine: historical overview and future prospects. Cell. 2019;8:1530.
18. Giannoudis P, Jones E, Yang X, Mcgonagle D. Mesenchymal stem cells and skeletal regeneration. Academic Press 2013.
19. Squillaro T, Peluso G, Galderisi U. Clinical trials with mesenchymal stem cells: an update. Cell Transplant 2016;25:829-48.
20. Abou Saleh H, Zouein F, El Yazbi A, et al. The march of pluripotent stem cells in cardiovascular regenerative medicine. Stem Cell Research Ther. 2018;9:201.
21. Nakamura K, Murry CE. Function follows form - a review of cardiac cell therapy. Circ J. 2019;83:2399-412.
22. Psaltis P, Schwarz N, Toledo Flores D, Nicholls SJ. Cellular therapy for heart failure. Curr Cardiol Rev.2016;12:195-215.
23. Van Berlo JH, Kanisicak O, Maillet M, et al. C-kit+ cells minimally contribute cardiomyocytes to the heart. Nature 2014;509:337-41.
24. Acar M, Kocherlakota KS, Murphy MM, et al. Deep imaging of bone marrow shows non-dividing stem cells are mainly perisinusoidal. Nature. 2015;526:126-30.
25. Menasche P. Cell therapy for heart regeneraion: lessons learned and future directions. Nat Rev Cardiol 2018:15:659-71.
26. Hudson W, Collins MC, deFreitas D, et al. Beating and arrested intramyocardial injections are assosiated with significant mechanical loss: implications for cardiac cell transplantation. J Surg Res 2007;142:263-7.
27. Laham RJ, Post M, Rezaee M, et al. Transendocardial and transepicardial intramyocardial fibroblast growth factor-2 administration: myocardial and tissue distributional. Drug Metab Dispos. 2005;33:1101-7
28. Chao W, Jingzhao L, Boya Z, Yongjian L. Safety and efficacy of bone marrow-derived cell therapy on cardiomyopathy: a meta-analysis. Stem Cell Research Ther. 2019;10:137
29. Terashvili M, Bosnjak ZJ. Stem cell therapies in cardiovascular disease. J Cardiothorac Vasc Anesth 2019:33:209-22.