Proceedings of ICBioMed 2024 Workshop: Workshop on Intelligent Medical Data Analysis for Precision Medicine
DOI: 10.54254/2753-8818/54/2024AU0116

New avenues in the treatment of ischemic heart disease - Stem cell therapy

Xiaolong Guo[1,3], Xuewu Zhang[2], Junkai Gou[2], Wenhui Li[1], Xi Chen[1]

[1]School of Stomatology, Lanzhou University, Lanzhou, Gansu, 730000, China
[2]The First Clinical College, Zunyi Medical University, Zunyi, Guizhou, 563099, China

[3]guoxl19@lzu.edu.cn

Abstract. Faced with the large number of patients with ischemic heart disease and high mortality rates, traditional drug treatments come with the risks of drug resistance and rebound effects after discontinuation, as well as the shortcomings of surgical treatments such as poor blood circulation and the inability to restore necrotic myocardium. This article starts from the perspective of stem cell regenerative medicine, focusing on the stem cell therapy for ischemic heart disease, and provides a comprehensive review of the types of stem cells and transplantation methods. It also includes further summaries and prospects, believing that more comprehensive and improved treatment methods will emerge in the future to benefit patients.

Keywords: Ischemic Heart Disease, Stem Cells, Cell Transplantation.

1. Introduction

Ischemic heart disease (IHD) is seeing an increase in both incidence and mortality rates annually. This condition has become one of the leading causes of death globally, especially in the United States, where it accounts for approximately 30% of deaths among people over the age of 35 [1]. In China, cardiovascular diseases cause about 3.5 million deaths per year, with over 30% of these deaths attributed to ischemic heart disease [2]. Recently, Professor Liang Xiaofeng‘s team from the Chinese Center for Disease Control and Prevention published a study in The Lancet, indicating that the mortality rate of ischemic heart disease has risen from the third to the second highest, increasing by 20.6% from 1990, and this trend continues [3].

2. Cell Therapy for Ischemic Heart Disease

Current treatment methods primarily encompass medication, interventional procedures, and surgical operations. However, traditional treatments still have significant drawbacks. In the exploration of new therapeutic approaches, innovative methods such as gene therapy and precision medicine have been included, offering potential solutions. Particularly in bioengineering, stem cell therapy is utilized to repair cardiomyocytes, aiming to overcome the limitations of existing treatments. For a long time, it was traditionally believed that the locally infarcted myocardial cells in ischemic heart disease could not regenerate, leading to hypertrophy of the remaining myocardial cells, proliferation of fibroblasts, and potentially causing heart failure over time [4]. However, at the 2004 AHA Scientific Session, researchers reported that almost all tissue and organ damage, aging, and degenerative diseases in the

DOI: 10.54254/2753-8818/54/2024AU0116

body could be treated with stem cells. Therefore, in the medical field, stem cells are also referred to as "universal cells" [5].

3. Stem Cells Mainly Used for the Treatment of Ischemic Heart Disease

3.1. Skeletal Muscle-Derived Stem Cells

Skeletal muscle myoblasts are cells with robust proliferative capabilities, capable of autologous transplantation, and can improve cardiac function after being injected into the myocardium [6]. However, since they differentiate into skeletal muscle cells rather than cardiomyocytes, there is an issue of ineffective electrophysiological integration with surrounding myocardial cells, which may lead to arrhythmias. To address this, researchers have adopted 3D catheter technology. This technique allows for more precise positioning of cells into specific areas of the heart, particularly within damaged myocardial scar tissue. Through this method, researchers can improve the left ventricular function of the heart while reducing the risk of arrhythmias [7].

Future research may focus on enhancing cell integration capabilities, preventing arrhythmias, and assessing long-term efficacy and safety. With these research advancements and technological progress, cell transplantation technology is expected to offer more effective treatment options for heart disease patients.

3.2. Embryonic Cardiac Cells/Embryonic Stem Cells

The research and application of embryonic stem cells (ESCs) represent a significant advancement in the field of regenerative medicine. In 2009, the U.S. Food and Drug Administration approved the first phase of clinical trials using human embryonic stem cell (hESC)-derived oligodendrocyte progenitor cells for the treatment of spinal cord injuries. This marked a significant breakthrough in the application of hESC therapy [8].

Researchers such as Mancuso found in vitro that hESCs can produce angiogenic and anti-apoptotic factors via paracrine mechanisms, which aid in promoting neovascularization, anti-apoptosis, and reducing myocardial fibrosis. This discovery has provided new therapeutic mechanisms for heart disease and other conditions [9].

In a clinical trial, researchers like Menasche embedded hESC-derived cardiac progenitor cells in fibrin patches. The results indicated an increase in the contractile function of the cardiac cell treatment area in patients, along with an improvement in symptoms [10].

3.3. Cardiac Stem Cells

The discovery and clinical application research of cardiac stem cells (CSCs) offer new hope for the treatment of cardiac diseases, especially ischemic cardiomyopathy. The utilization of these stem cells reflects the significant progress of regenerative medicine in the field of heart disease treatment.

In 2001, research by Beltrami and colleagues at the New York Medical College first demonstrated the presence of cardiac stem cells in the myocardium [11]. This discovery altered the previous notion that cardiomyocytes in the adult heart could not regenerate, paving the way for new avenues in heart disease treatment. In 2011, Bolli and colleagues published their research findings in The Lancet, reporting the first phase of clinical trials for the clinical application of CSCs. In the study, autologous CSCs were transplanted via the coronary artery to treat ischemic cardiomyopathy. The results showed that the left ventricular ejection fraction (LVEF) in patients with a history of myocardial infarction was effectively improved in both short-term and long-term efficacy assessments, with a 24% reduction in the infarct size [12].

3.4. Bone Marrow-Derived Stem Cells

Bone marrow stem cells are the cornerstone of the blood and immune systems, possessing high therapeutic potential, especially in the fields of regenerative medicine and transplant medicine. These stem cells are crucial for their abilities and functions within the body, involving the generation of

DOI: 10.54254/2753-8818/54/2024AU0116

multiple cell types and the treatment of diseases. They mainly include hematopoietic stem cells (HSCs), endothelial progenitor cells (EPCs), mesenchymal stem cells (MSCs), and bone marrow mononuclear cells, among others. Research and clinical applications of bone marrow stem cells are continuously evolving, and with a deeper understanding of these cells and their microenvironment, more innovative and effective treatment strategies may be developed in the future.

3.4.1. Endothelial Progenitor Cells

Endothelial progenitor cells (EPCs) were first discovered by Asahara and colleagues. They isolated CD34+ cells from human circulating blood, which can differentiate into cells with endothelial characteristics in vitro [13].

In terms of clinical application, EPCs have shown tremendous potential, especially in the treatment of ischemic heart disease. By using factors such as vascular endothelial growth factor (VEGF) that promote angiogenesis, EPCs can be attracted to ischemic areas and participate in the formation of new blood vessels [14]. This characteristic makes them an ideal target cell for gene therapy of cardiovascular diseases [15].

As a cell type with the potential for self-renewal and vascular repair, EPCs play an increasingly important role in cardiovascular regenerative medicine. With ongoing research and technological innovation, EPCs are expected to bring breakthroughs in treatment for more patients in the near future.

3.4.2. Hematopoietic Stem Cells (HSCs)

Hematopoietic stem cells (HSCs) are a rare type of cell found in bone marrow, capable of generating all types of blood cells. These cells play a key role in regenerative medicine and the treatment of various blood disorders. Studies have shown that HSCs can improve cardiac function and slow ventricular remodeling after myocardial infarction through paracrine effects. This effect is mainly achieved by stimulating neovascularization, inhibiting cell apoptosis, recruiting cardiac progenitor cells, and altering the composition of the extracellular matrix [16]. Future research may explore more about the mechanisms of HSCs in the treatment of cardiac diseases and optimize their treatment strategies to improve their clinical usability and effectiveness.

3.4.3. Bone Marrow Mesenchymal Stem Cells (MSCs)

Research on mesenchymal stem cells (MSCs) has demonstrated their multifaceted potential in the treatment of cardiac diseases, especially in cardiac repair and the improvement of cardiac function through paracrine mechanisms. Early studies suggested that MSCs could improve cardiac function by transdifferentiating into cardiomyocytes, but recent research indicates that MSCs mainly promote neovascularization by secreting cytokines and angiogenic growth factors [17]. In addition, MSCs can inhibit T-cell proliferation and immune responses through cell-cell interactions and the cytokines they produce, which is crucial for reducing inflammation and improving ventricular remodeling after cardiac disease [18].

In a study by Mangi et al., MSCs with the Akt1 gene transduced by viral vectors were implanted into the myocardium of rats with acute myocardial infarction (AMI), and the results showed that these MSCs could inhibit ventricular remodeling by reducing inflammation, collagen deposition, and cardiomyocyte hypertrophy [19]. Oswald et al. confirmed that human bone marrow-derived MSCs can expand and differentiate into cells with endothelial phenotypes and functions under specific culture conditions, highlighting the potential of MSCs as a source for transplantation [20].

Stem cells can secrete a variety of cytokines. In addition to inhibiting host cell apoptosis and promoting the formation of new blood vessels, some factors may also promote the migration and differentiation of cardiomyocytes. Urbanek et al. found that after myocardial infarction, locally administered hepatocyte growth factor (HGF) and insulin-like growth factor (IGF-1) can promote the migration of cardiomyocytes from outside the infarction area to the infarction area, forming new cardiomyocytes and blood vessels [21].

DOI: 10.54254/2753-8818/54/2024AU0116

These research results highlight the potential of MSCs in the treatment of heart disease, especially their ability to promote cardiac repair, improve cardiac function, and reduce inflammation through immunomodulatory mechanisms. Future research may further optimize the therapeutic strategies of MSCs to enhance their therapeutic effects and safety.

3.5. Genetically Engineered Stem Cells

Genetic modification provides a new opportunity for the treatment of ischemic heart disease with stem cells, playing a significant role in protecting the survival of stem cells in the body, improving the efficiency of stem cell delivery platforms, and tracking stem cells within the body. Transfecting the integrin-linked kinase gene into MSCs can enhance their adhesion to ischemic myocardium, reduce infarct size and fibrosis, and promote microvascular formation, which is beneficial for the repair of damaged myocardium [22]. In addition, heme oxygenase-1 (HO-1) is another protective gene that promotes cell survival by inhibiting high-mobility group protein 1 in inflammatory and endotoxemic environments. MSCs transfected with HO-1 can increase the density of capillaries and small arteries in the peri-infarct area, and their long-term survival rate in the body is significantly improved [23].

Genetically modified MSCs can effectively regulate the expression of factors or proteins of interest to medical workers, and the expressed bioactive substances have long-term benefits, enhancing the therapeutic effects of MSCs. However, the safety of genetically modified MSCs has become an important factor limiting their large-scale clinical application, and further research from the basic to clinical level is still needed to maximize benefits and minimize risks.

4. Stem Cell Transplantation Methods

The successful implementation of CCT requires the injection of a high concentration of cells into the target area. Therefore, local transplantation cell injection is superior to systemic cell injection. Available routes include intracoronary injection, transendocardial injection, transepicardial injection, and injection via the coronary veins [24].

4.1. Intracoronary Injection

Intracoronary injection is the most widely used transplantation method [25]. Its advantages include the ability to directly administer cells during interventional treatment without special equipment, transplanting cells to the target myocardial area through the target vessel; arterial transplantation also ensures that the transplanted cells have a blood supply. However, this method of inputting cell solution under high pressure can damage cells and, like endocardial injection and myocardial injection, may cause arrhythmias [26].

4.2. Transendocardial Injection via Percutaneous Catheter

Transendocardial injection requires special equipment (endocardial electromechanical mapping system) [27] and is more complex. Transendocardial injection via percutaneous catheter refers to the use of an injection catheter to cross the aortic valve and is placed on the endocardial surface, with cells being directly injected into the left ventricular wall. Perin et al. [27] selected 21 patients with chronic severe heart failure caused by ischemic heart disease and non-randomly divided them into two groups. The transplantation method used transendocardial injection via percutaneous catheter to inject autologous bone marrow mononuclear cells, resulting in a reduction in left ventricular end-systolic volume and improved blood supply in the injection area.

4.3. Direct Epicardial Injection

Direct epicardial injection has been used as an adjunctive treatment for coronary artery bypass grafting (CABG). During open-heart surgery, the infarct area can be directly visualized, and cells can be accurately injected into the scar area or the border zone of the scar. The invasiveness of this method limits it as a standalone treatment approach. Conversely, if CABG surgery is performed simultaneously, evaluating and determining the efficacy of cell transplantation will be challenging.

DOI: 10.54254/2753-8818/54/2024AU0116

Epicardial injection of bone marrow mononuclear cells is usually a supplementary treatment for CABG.

4.4. Peripheral Venous Implantation

Kocher et al. [28] confirmed that by dripping human CD34+ bone marrow mononuclear cells into the tail vein of nude mice, they could migrate to the myocardial infarction lesion, leading to new blood vessel formation at the infarction site in rats without CD34+, improving cardiac function. Compared to local puncture and arterial approaches, this method is safer and less invasive. The downside is that it requires a larger amount of cells and may enter non-target organs. The efficiency of peripheral venous injection is lower than other transplantation methods, and its effectiveness is controversial. Some studies have shown that no transplanted homing stem cells were found in the infarcted myocardium [29].

4.5. "Self-Transplantation" Method Established Using the "Homing" Characteristics of Bone Marrow Stem Cells

Orlic et al. [30] used injections of human granulocyte colony-stimulating factor (G-CSF) and stem cell factor (SCF) to confirm the "self-transplantation" method established using the "homing" characteristics of bone marrow stem cells. This method is non-invasive and does not require the separation, collection, and reinfusion of stem cells, nor does it face the difficulties in sourcing and immune rejection associated with allogeneic stem cell transplantation, thus offering great application prospects.

5. Conclusion and Prospects

The exploration of stem cell therapy for ischemic heart disease (IHD) is indeed a research field full of hope but also full of challenges. With in-depth scientific research, stem cell therapy offers a potential treatment path, especially in complex disease conditions that traditional treatment methods cannot fully resolve. In future research directions, the verification of the safety and efficacy of stem cell therapy can be achieved by improving biomarkers and imaging technology, cell engineering and gene editing, developing new transplantation techniques, and implementing larger multicenter clinical trials. Although there are many challenges in stem cell therapy for IHD, these issues are expected to be resolved with in-depth research and technological development, making stem cell therapy an effective means of treating heart disease and better benefiting the majority of patients with ischemic heart disease.

References

[1] Xu, J., et al. Mortality in the United States, 2018. NCHS Data in Brief, 2020(355), 1–8.
[2] MichlerRE.The current status of stem cell therapy in ischemic heart.disease[J].J Cardiac Surgery, 2018, 33(9):520-531.
[3] Zhou M, Wang H, Zeng X, et al.Mortality, morbidity, and risk factors in China and its provinces, 1990-2017:a systematic analysis for the Global Burden of Disease Study 2017[J].Lancet, 2019, 394(10204):1145-1158.
[4] SACCARO LF, AIMO A, EMDIN M, et al.Remote Ischemic Conditioning in Ischemic Stroke and Myocardial Infarction:Similarities and Differences.Front Neurol.2021;12:716316.
[5] LIU C, HAN D, LIANG P, et al.The Current Dilemma and Breakthrough of Stem Cell Therapy in Ischemic Heart Disease.Front Cell Dev Biol.2021;9:636136.
[6] Rubart M, Soonpaa MH, Nakajima H, et al.Spontaneous and evoked intracellular calcium transients in donor-derived myocytes following intracardiac myoblast transplantation.J Clin Invest.2004, 114 (6) :775-83.
[7] Li SH, Lai TY, Sun Z, et al.Tracking cardiac engraftment and distribution of implanted bone marrow cells:Comparing intraaortic, intravenous, and intramyocardial delivery.J Thorac Cardiovasc Surg.2009, 137 (5) :1225-33.

DOI: 10.54254/2753-8818/54/2024AU0116

[8] Eguizabal C, Aran B, Chuva de Sousa Lopes SM, et al.Two decades of embry on icstemcells: ahistorical overview[J].Hum Reprod, 2019, 2019(1):3-4.
[9] Mancuso P, Raman S, Glynn A, et al.Mesenchymal stem cell therapy for osteoarthritis:the critical role of the cell secretome[J].Front Bioeng Biotechnol, 2019, 7:9.
[10] Menasché P, Vanneaux V, Hagège A, et al.Transplantation of human embryonic stem cell-derived cardiovascular progenitors for severe ischemic left ventricular dysfunction[J].J Am College Cardiol, 2018, 71(4):429-438.
[11] Beltrami AP, Urbanek K, Kaistura JL, et al.Evidence thathuman cardiac myocytes divide after myocardial infarction[J].N Engl J Med, 2001, 344 (23) :1750-1757.
[12] Bolli R, Chugh AR, D'Amario D, et al.Cardiac stem cellsin patients with ischaemic cardiomyopathy (SCIPIO) :initial results of a randomised phaseItrial[J].Lancet, 2011, 378 (9806) :1847-1857.
[13] Asahara T, Murohara T, Sullivan A, et al.Isolation of putative progenitor endothelial cells for angiogenesis.Science.1997, 275 (5302) :964-967.
[14] Asahara T, Masuda H, Takahashi T, et al.Bone marrow origin ofendothelial progenitor cells responsible for postnatal vasculogenesisin physiological and pathological neovascularization[J].Circ Res, 1999, 85 (3) :221-228.
[15] Graham RM, Bishopric NH, Webster KA, et al.Gene and celltherapy for heart disease[J].IUBMB Life, 2002, 54 (2) :59-66.
[16] Jan VR, Sander FR, Martin JS, et al.Bone Marrow Cell Injection for Chronic Myocardial Ischemia:The Past and the Future.J CardiovascTrans Res.2011, 4 (2) :182-191.
[17] Mirotsou M, Zhang Z, Deb A, et al.Secreted frizzled related protein 2 (Sfrp2) is the key Akt-mesenchymal stem cell-released paracrine factor mediating myocardial survival and repair. ProcNatlAcadSci USA.2007, 104 (5) :1643-1648.
[18] Le BK, Ringden O.Immunomodulation by mesenchymal stem cells and clinical experience. Journal of Internal Medicine.2007, 262 (5) :509-525.
[19] Mangi AA, Noiseux N, kong D, et al.Nat Med, 2003:9 (9) :1195-1201.
[20] Oswald J, Boxberger S, Jorgensen B, et al.Stem Cells, 2004;22 (3) :377-384.
[21] Urbanek K, Rota M, Cascapera S, et al.Cardiac stem cells possess growth factor-receptor systems that after activation regenerate the in-farcted myocardium, improving ventricular function and long-term sur-vival[J].Cire Res2005, 97:663-673.
[22] ZENG B, LIU L, WANG S F, et al.ILK regulates MSCs survival and angiogenesis partially through AKT and mTOR signaling pathways[J].ActaHistochem, 2017, 119(4):400-406.DOI: 10.1016/j.acthis.2017.04.003
[23] SUN D, SONG H L, SHEN Z Y.Research progress in mesenchymal stem cells modified by Heme oxygenase 1[J].Chin J Reparative ReconstrSurg, 2019, 33(7):901-906.DOI:10.7507/1002-1892.201812079.
[24] Sheng CC, Zhou L, and Hao J.Current stem cell delivery methods for myocardial repair[J]. Biomed Res Int, 2013, 2013:547902.
[25] Gao LR, Wang ZG, Zhu ZM, et al.Effect of intracoronarytransplantation of autologous bone marrow-derived mono-nuclear cells on outcomes of patients with refractory chro-nic heart failure secondary to ischemic cardiomyopathy[J].Am J Cardiol, 2006, 98 (5) :597-602.
[26] Tse HF, Kwong YL, Chan JK, et al.Angiogenesis in ischaemicmyocardium by intramyocardial autologous bone marrowmononuclear cell implantation[J].Lancet, 2003, 361 (9351) :47-49.
[27] Perin EC, Dohmann HF, Borojevic R, et al.Transendocar-dial, autologous bone marrow cell transplantation for se-vere, chronic ischemic heart failure[J].Circulation, 2003, 107 (18) : 2294-2302.
[28] Kocher AA, SchusterMD, Szabolcs M I, et al.Neovascu larization ofischem ic myocard ium by human bone-marrow-derived angiob lastsprevents card iomyocyte apoptosis, reduces remodeling and improvescard iac function[J].NatM ed, 2001, 7 (4) :430-6.

DOI: 10.54254/2753-8818/54/2024AU0116

[29] Barbash IM, Chouraqui P, Baron J, et al.Systemic deliveryof bone marrow-derived mesenchymal stem cells to the in-farcted myocardium:feasibility, cell migration, and bodydist ribution[J]. Circulation, 2003, 108 (7) :863-868.

[30] O rlic D, Kajstura J, Ch im enti S, et a.l Mob ilized bone marrow cellsrepair the infarcted heart, improving function and survival[J].ProcNatl Acad Sci USA, 2001, 98 (18) :10344-9.