Education

E-ISSN No : 2581-6195 | Volume : 7 | Issue : 4 | April 2024

ADVANCEMENTS IN STEM CELL THERAPY FOR CARDIOVASCULAR DISEASES

Christa Kudaverdian

ABSTRACT

This comprehensive review navigates the landscape of cardiovascular regenerative medicine, focusing on the pivotal role of stem cell therapy and tissue engineering. Stem cells, versatile in differentiation capacities, are categorized into embryonic and non-embryonic types, such as hematopoietic and mesenchymal stem cells. Despite classifications, these cells share the fundamental features of boundless self-renewal, asymmetric divisions, and irreversible differentiation. The exploration begins with the backdrop of cardiovascular diseases as a leading cause of mortality, motivating extensive research into myocardial regeneration and repair. Stem cell therapy, emerging a decade ago, seeks to activate endogenous regenerative mechanisms, particularly in conditions like Acute Myocardial Infarction (AMI). In the context of AMI, the narrative unfolds through trials involving Bone Marrow Mononuclear Cells (BMMNCs), showcasing conflicting outcomes and prompting a shift toward Mesenchymal Stem Cells (MSCs). Trials with allogeneic MSCs, including those from umbilical cord sources, show promise in reducing scar size and enhancing Left Ventricular Ejection Fraction (LVEF). Investigations into Wharton's jelly-derived MSCs further emphasize their benefits in a mini-swine AMI model, indicating survival, differentiation, and positive effects on ventricular remodeling. Ischemic Cardiomyopathy studies, detailed in JAMA, highlight the safety and efficacy of both autologous and allogeneic stem cells, with the latter offering off-the-shelf therapeutic potential, simplifying treatment regimens. The prospect of Tissue Engineered Heart Valves using cryopreserved CD133(+) cells from umbilical cord blood showcases a noteworthy stride in generating viable human heart valves. This involves a meticulous process of expansion, differentiation, and phenotypic analysis within biodegradable polymer scaffolds, promising a symphony of regenerative possibilities. In conclusion, this exploration reveals groundbreaking revelations in cardiovascular medicine, presenting a beacon of hope through the amalgamation of stem cell therapy, innovative trials, and tissue engineering. The symphony of regeneration, conducted by stem cells and engineered tissues, resonates with the promise of a healthier, regenerated heart, marking a significant stride in medical progress.

[1] Research Scholars Program, Harvard Student Agencies, In collaboration with Learn with Leaders

HOW TO CITE THIS ARTICLE:
Christa Kudaverdian (2024). Advancements In Stem Cell Therapy For Cardiovascular Diseases, International Educational Journal of Science and Engineering (IEJSE), Vol: 7, Issue: 4, 01-05

INTRODUCTION

Stem cells exhibit the capacity to differentiate into cells of the same type, which subsequently give rise to various cell types. These cells can be categorized based on their origin and their potential for differentiation. Origin-wise, stem cells fall into two main types: embryonic stem cells (ESCs) and non-ESCs. Non-ESCs, in turn, manifest as Haematopoietic Stem Cells (HSCs) that differentiate into diverse blood cells and carry the CD34+ marker, and the less differentiated Mesenchymal Stem Cells (MSCs). Another classification system designates stem cells as totipotent, pluripotent, or multipotent, depending on their ability to differentiate into distinct cell types. Regardless of classification, all stem cells share three common features: boundless self-renewal capacity, the potential for asymmetric divisions, and an irreversible differentiation process.

In Western countries, cardiovascular diseases stand as the leading cause of mortality. Unlike lower vertebrates such as zebrafish, adult mammals lack the inherent capacity for natural heart regeneration throughout their lives [1]. Consequently, extensive research has explored therapeutic approaches for myocardial regeneration and repair. Stem cell therapy emerged as a promising strategy, with the initial clinical trials about a decade ago endorsing its potential in treating these disorders. Current research in cardiac regenerative medicine aims to activate endogenous regenerative mechanisms through cell therapy, particularly in conditions like Myocardial Infarction (AMI), Ischemic Cardiomyopathy, and Tissue Engineered Heart Valves. This involves a combination of two components: a cardiomyocyte source serving as the regeneration target and a non-myocardial tissue acting as a regeneration source within an optimal cardiac environment.

LITERATURE REVIEW

Stem cell-based therapies have emerged as a promising approach for cardiac regeneration,

Research Paper

Copyright© 2024, IEJSE. This open-access article is published under the terms of the Creative Commons Attribution-NonCommercial 4.0 International License which permits Share (copy and redistribute the material in any medium or format) and Adapt (remix, transform, and build upon the material) under the Attribution-NonCommercial terms.

aiming to repair and replace damaged myocardium. While adult stem cells, particularly Mesenchymal Stem Cells (MSCs), have shown notable potential, Pluripotent Stem Cells (PSCs) offer unique advantages due to their unlimited differentiation capabilities. This literature review discusses the progress, challenges, and alternative strategies in the use of adult and pluripotent stem cells for cardiac regeneration. The review begins by highlighting the significance of adult stem cells, emphasizing the ethical advantages of using them over embryonic stem cells. Skeletal myoblasts, initially explored for cardiac regeneration, demonstrated potential in regenerating skeletal muscle but faced challenges in fully restoring heart function. Bone marrow-derived progenitor cells, such as Hematopoietic Stem Cells (HSCs) and Endothelial Progenitor Cells (EPCs), showed varying results in clinical trials for both ischemic and non-ischemic cardiomyopathies. The focus then shifts to MSCs, which have become a central player in regenerative medicine. MSCs, derived from various tissues and organs, exhibit multipotent differentiation capabilities, including the ability to differentiate into functional cardiomyocytes. The literature review discusses studies showcasing MSC engraftment, cardiomyogenesis, and improved cardiac functions in animal models. However, it notes a clinical trial with no beneficial effect upon intravenous injection of MSCs, emphasizing the importance of delivery methods in achieving positive outcomes. The discussion extends to pluripotent stem cells, particularly human Embryonic Stem Cells (ESCs) and induced Pluripotent Stem Cells (iPSCs). While PSCs offer an unlimited source of cardiomyocytes, challenges related to their immature phenotype and heterogeneity arise [2]. Differentiation protocols, including embryoid body formation and refined signaling factor manipulation, are explored. The review emphasizes the need for precise evaluation using non-human primate models to bridge the gap between animal studies and human applications. In light of the challenges associated with PSC-CMs, the review discusses alternative strategies for cardiac regeneration. It explores cell-free approaches, focusing on the paracrine effects of stem cells, growth factor therapy, modified mRNA, and stem cell-derived exosomes. The potential of exosomes to deliver bioactive molecules and stimulate endogenous repair mechanisms is highlighted.

Acute Myocardial Infarction

Cell-based therapy in clinical medicine originated predominantly from trials investigating Acute Myocardial Infarction (AMI) [3]. The objective was to utilize intracoronary stem cell infusion alongside percutaneous coronary intervention, a strategy known as cardioprotection, to mitigate cardiomyocyte necrosis and impede Heart Failure (HF) progression. Bone Marrow Mononuclear Cells (BMMNCs) are commonly employed, harvested post-intervention, and swiftly reinfused without requiring culture expansion. Early trials, such as TOPCARE-AMI and BOOST, demonstrated promising results in terms of Left Ventricular Ejection Fraction (LVEF) improvement and cardiac remodeling [4]. However, subsequent studies like TIME, LateTIME, SWISS AMI, and BOOST-2 produced conflicting outcomes, questioning the efficacy of BMMNCs. The REPAIR-AMI study, a phase III trial, revealed significant improvements in LVEF and reduced adverse events at 1 year, but conflicting results emerged in later years. Despite the mixed findings, CD34+ endothelial progenitors from BMMNCs were explored for their angiogenic potential in the PreSERVE-AMI study, indicating dose-dependent benefits. Heterogeneity in early AMI trials underscores the need for standardized techniques in cell handling and imaging methods, with cMRI emerging as a preferred assessment tool. Recent BMMNC trials, including the ongoing BAMI trial, suggest limited efficacy, prompting exploration of alternative cell types like Mesenchymal Stem Cells (MSCs) [4]. Allogeneic MSC trials, such as those using umbilical cord–derived MSCs, demonstrate promise in reducing scar size and enhancing LVEF. Ongoing trials, like CAREMI and AMICI, further investigate the potential of allogeneic CSCs and mesenchymal precursor cells in AMI therapy.

Further investigation on mesenchymal cells was conducted. Wharton's jelly-derived mesenchymal stem cells (WJ-MSCs), isolated from human umbilical cord tissue under sterile conditions, were expanded up to passage 5 and labeled with CM-Dil before transplantation. Using a mini-swine AMI model, the left anterior descending artery was surgically ligated. Miniswine was randomly assigned to three groups (n=6 each): control, PBS, and transplantation. After six weeks, single-photon emission computed tomography and echocardiography assessed changes in myocardial perfusion and function. Animals were then euthanized, and histopathological examination of infarcted tissues revealed significant improvements in the transplantation group ($P<0.001$) [6]. Transplanted WJ-MSCs survived and differentiated into cardiomyocytes and endothelial cells. Resident cardiac stem cells also contributed to this differentiation. Masson's trichrome staining indicated more viable myocardium and less fibrous tissue in the transplantation group ($P<0.001$), accompanied by increased vessel density and reduced cell apoptosis ($P<0.001$). In conclusion, direct WJ-MSC injection into the infarcted area resulted in survival, differentiation, and beneficial effects on ventricular remodeling and function in a miniswine AMI model [7].

Ischemic Cardiomyopathy

Utilizing stem cells for the revitalization of compromised cardiac tissue in individuals contending with chronic heart failure not only attests to its safety but also unveils substantial advantages. A pioneering study, led by researchers from Johns Hopkins University School of Medicine and the University of Miami Miller School of Medicine, meticulously chronicled in the Journal of the American Medical Association (JAMA), conducted a nuanced examination of autologous stem cells (derived from the patients' own bone marrow) against allogeneic stem cells (sourced from healthy volunteer donors) within the realm of treating ischemic cardiomyopathy [8].

This avant-garde therapeutic paradigm notably reduced scar tissue within the heart muscles, markedly enhanced the quality of life for patients, and, in many instances, augmented cardiac pumping capabilities. Representing a seminal achievement, this inaugural study emphasized the safety of both autologous and allogeneic stem cells within a 30-day treatment framework. The distinctive merit of allogeneic cells lies in their potential for

off-the-shelf therapeutic applications, obviating the need for invasive bone marrow biopsies from heart failure patients and simplifying the treatment regimen.

The utilization of mesenchymal stem cells in this therapeutic framework further distinguishes itself by minimizing the likelihood of provoking immune responses and rejection, highlighting its potential for efficacious cardiac tissue repair and inflammation mitigation. The study, characterized by meticulous monitoring, unveiled a notable absence of treatment-related fatalities, heart attacks, or adverse events over a 12-month period, auguring well for the advancement of stem cell therapy in addressing advanced heart failure [9].

Prospective avenues of inquiry will delve into comparative studies against placebos, a scrutiny of the cumulative effects of repeated doses, and a comprehensive examination of the safety and efficacy of stem cell therapy for heart failure emanating from alternative causes. This research, with its groundbreaking revelations, heralds a promising trajectory for the evolution of sophisticated treatments in the realm of cardiovascular medicine [10].

Tissue Engineered Heart Valves

The prospect of advancing medical frontiers through the tissue engineering of autologous heart valves capable of growth and remodeling holds substantial promise. The investigation delves into the innovative application of cryopreserved CD133(+) cells derived from umbilical cord blood as an exclusive cellular reservoir for engineering heart valves. The methodology involved a meticulous process of expanding and differentiating CD133(+) cells, followed by a comprehensive analysis of their phenotypes through immunohistochemistry before cryopreservation. Heart valve scaffolds, consisting of a biodegradable polymer (n = 8), were subsequently populated with blood-derived myofibroblasts and enveloped with blood-derived endothelial cells [11]. The ensuing development of these tissue-engineered heart valve constructs took place within a pulse duplicator system. An exhaustive examination unfolded, encompassing histological scrutiny, immunohistochemical assessments, electron microscopic exploration, fluorescence imaging, and detailed biochemical and biomechanical evaluations. The tissue-engineered heart valves displayed the intricate formation of endothelialized layered tissue, illustrating the seamless integration of connective tissue across the entire scaffold. Validation of the endothelial phenotype's integrity was fortified by fluorescence imaging studies, highlighting cellular nitric oxide production and Ca(2+) signaling. Electron microscopy illuminated the infiltration of cells into the scaffold's interstices, forming a coherent tissue layer. Biochemical analysis unveiled the development of an extracellular matrix (77% +/- 9% collagen of human pulmonary leaflet tissue [HPLT], 85% +/- 61% glycosaminoglycans of HPLT, and 67% +/- 17% elastin of HPLT) [12]. The study conducted by the Department of Cardiovascular Surgery at Ludwig-Maximilians-University in Munich, Germany represents a noteworthy stride forward, showcasing the in vitro generation of viable human heart valves utilizing CD133(+) cells derived from umbilical cord blood. The findings signify a pivotal advancement in the refinement of clinical strategies for addressing congenital defects and hold auspicious implications for the evolution of cutting-edge approaches in regenerative medicine.

CONCLUSION

The exploration of stem cells in cardiovascular medicine unveils a nuanced landscape of potentialities and challenges. Stem cells, characterized by their boundless self-renewal capacity and differentiation potential, present a diverse array categorized by origin and differentiation capabilities. From embryonic stem cells to haematopoietic and mesenchymal stem cells, the classification underscores the profound versatility inherent in these cellular entities.

The application of stem cells in the context of cardiovascular diseases, especially in the aftermath of acute myocardial infarction (AMI) and ischemic cardiomyopathy, has been both pioneering and intricate. While early trials with Bone Marrow Mononuclear Cells (BMMNCs) showed promise, subsequent studies revealed conflicting outcomes, prompting a quest for alternative cell types such as Mesenchymal Stem Cells (MSCs). Ongoing trials, like CAREMI and AMICI, delve into the potential of allogeneic CSCs and mesenchymal precursor cells, signifying a dynamic evolution in therapeutic strategies. The investigation into Wharton's jelly-derived mesenchymal stem cells (WJ-MSCs) in a mini-swine AMI model provides a noteworthy advancement, showcasing the survival, differentiation, and beneficial effects on ventricular remodeling and function. The intricate interplay between transplanted WJ-MSCs and resident cardiac stem cells highlights the multifaceted potential of stem cell therapy in addressing the complex aftermath of AMI.

In the realm of ischemic cardiomyopathy, the differentiation between autologous and allogeneic stem cells opens new frontiers. The reduction of scar tissue, improvement in quality of life, and enhanced cardiac pumping capabilities underscore the therapeutic potential of stem cells. The safety profile within a 30-day treatment framework, coupled with the off-the-shelf potential of allogeneic cells, presents a paradigm shift in treatment regimens.

The exploration of tissue-engineered heart valves further amplifies the horizon of possibilities. The meticulous engineering of heart valves using cryopreserved CD133(+) cells from umbilical cord blood showcases a groundbreaking approach. The development of endothelialized layered tissue and the formation of a coherent tissue layer within the scaffold represent a substantial stride forward. This innovative strategy, exemplified by the study from Ludwig-Maximilians-University in Munich, holds promise for addressing congenital defects and propelling regenerative medicine into uncharted territories.

As we stand at the intersection of stem cell research and cardiovascular medicine, the journey ahead involves standardized techniques, comparative studies, and comprehensive examinations of safety and efficacy. The revelations from these studies not only augur well for addressing the intricacies of cardiovascular disorders but also herald a promising trajectory

for the evolution of sophisticated treatments in the realm of regenerative medicine. The dynamic interplay between stem cells and cardiac tissues opens avenues for transformative interventions, paving the way for a future where cardiovascular diseases may find innovative and effective solutions.

ACKNOWLEDGEMENTS

This has been one of the most humbling experiences of my life. I have been working on this research endeavor for 6 years now. I started first with researching stem cells and their effects on joints and arthritis when I was 12 years old. I then proceeded to expand my research into the field of cardiology because of my father. My dad had an open-heart operation after suffering from Coronary Artery Disease (CAD) and a minor heart. This prompted me to study unconventional therapies to improve my dad's condition, which is how I was introduced to stem cells. I want to extend my deepest gratitude to my family and close friends for continuously supporting me and believing in my skills to pursue this, I am eternally grateful. Thank you to the Learn with Leaders team and Harvard Student Agencies for this publication. Thank you for helping me take this all the way, I am very grateful. This is for my parents. Mama, Papa, thank you for always believing in me, even when I did not. Thank you for pushing me and standing by me no matter what, for always supporting my dreams, for the morals and life lessons that you have taught me, for teaching me right from wrong, and for making me the person I am today. No matter what I do and how much I say it, it will never be enough. You both are the lights of my life. Papa, you have patience that spans seas. You are the most selfless and strongest person I know, and you have the kindest heart. Mama, you are the most compassionate and strongest person I know, and you have the purest heart. You both have taught me that the most important thing is to be a good person who cares about people. I hope that I will grow to become like you both. You tell me that my education is a priority for you, thank you for giving me such an incredible education that has led me to this point. My only hope is that one day, I can do half as much as you have done for me. I love you with all my heart and all that I am.

CITATIONS

1. 1. Cardiac Regeneration - Center for Regenerative Biotherapeutics - Mayo Clinic Research. (n.d.). Mayo Foundation for Medical Education and Research. Retrieved November 18, 2023, from https://www.mayo.edu/research/centers-programs/center-regenerative-biotherapeutics/focus-areas/cardiac-regeneration
2. Cord Blood & Cord Tissue in the Treatment of Heart Disease. (n.d.). Cryo-Cell. Retrieved November 18, 2023, from https://www.cryo-cell.com/treatments-and-research/heart-disease
3. Curfman, G. (n.d.). Stem Cell Therapy for Heart Failure: An Unfulfilled Promise? PubMed. Retrieved November 18, 2023, from https://pubmed.ncbi.nlm.nih.gov/30912818/
4. Hare, J. M. (2018, May 25). Mesenchymal Stem Cell-Based Therapy for Cardiovascular Disease: Progress and Challenges. NCBI. Retrieved November 18, 2023, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6037203/
5. Heart Disease | Applications of Stem Cell Research | ISCRM. (n.d.). Institute for Stem Cell & Regenerative Medicine. Retrieved November 18, 2023, from https://iscrm.uw.edu/research/heart-disease/
6. Mending a broken heart: current strategies and limitations of cell-based therapy - Stem Cell Research & Therapy. (2020, March 26). Stem Cell Research & Therapy. Retrieved November 18, 2023, from https://stemcellres.biomedcentral.com/articles/10.1186/s13287-020-01648-0#Sec2
7. Repairing the heart with stem cells. (2013, March 1). Harvard Health. Retrieved November 18, 2023, from https://www.health.harvard.edu/heart-health/repairing-the-heart-with-stem-cells
8. Stem Cells to Regenerate Cardiac Tissue in Heart Failure. (n.d.). Revista Española de Cardiología. Retrieved November 18, 2023, from https://www.revespcardiol.org/en-stem-cells-regenerate-cardiac-tissue-articulo-13052403
9. Nagamura-Inoue, T., & He, H. (2014). Umbilical cord-derived mesenchymal stem cells: Their advantages and potential clinical utility. World journal of stem cells, 6(2), 195–202. https://doi.org/10.4252/wjsc.v6.i2.195
10. Wollert, K. C., & Drexler, H. (2005, February 4). Clinical Applications of Stem Cells for the Heart. Circulation Research. Retrieved November 18, 2023, from https://www.ahajournals.org/doi/10.1161/01.RES.0000155333.69009.63#d3e343
11. Zhang, Y., Mignone, J., & MacLellan, W. R. (2015, October 1). Cardiac Regeneration and Stem Cells. Physiological Reviews. https://journals.physiology.org/doi/full/10.1152/physrev.00021.2014

REFERENCE

1. Mesenchymal stem cells in cardiac regeneration: a detailed progress report of the last 6 years (2010–2015) - Stem Cell Research & Therapy. (2016, June 4). Stem Cell Research & Therapy. Retrieved November 18, 2023, from https://stemcellres.biomedcentral.com/articles/10.1186/s13287-016-0341-0
2. Mesenchymal stem cells in cardiac regeneration: a detailed progress report of the last 6 years (2010–2015) - Stem Cell Research & Therapy. (2016, June 4). Stem Cell Research & Therapy. Retrieved November 18, 2023, from https://stemcellres.biomedcentral.com/articles/10.1186/s13287-016-0341-0
3. Banerjee, M. N., Bolli, R., & Harre, J. M. (2018, July 6). Clinical Studies of Cell Therapy in Cardiovascular Medicine Recent Developments and Future Directions. Circulation Research. Retrieved November 18, 2023, from https://www.ahajournals.org/doi/10.1161/circresaha.118.311217#d1e664
4. Banerjee, M. N., Bolli, R., & Harre, J. M. (2018, July 6). Clinical Studies of Cell Therapy in Cardiovascular Medicine Recent Developments and Future Directions. Circulation Research. Retrieved November 18, 2023, from https://www.ahajournals.org/doi/10.1161/circresaha.118.311217#d1e664
5. Banerjee, M. N., Bolli, R., & Harre, J. M. (2018, July 6). Clinical Studies of Cell Therapy in Cardiovascular Medicine Recent Developments and Future Directions. Circulation Research. Retrieved November 18, 2023, from https://www.ahajournals.org/doi/10.1161/circresaha.118.311217#d1e664
6. Chen, Y. (2015, July 10). Intracoronary infusion of Wharton's jelly-derived mesenchymal stem cells in acute myocardial infarction: double-blind, randomized controlled trial - BMC Medicine. BMC Medicine. Retrieved November 18, 2023, from https://bmcmedicine.biomedcentral.com/articles/10.1186/s12916-015-0399-z
7. Chen, Y. (2015, July 10). Intracoronary infusion of Wharton's jelly-derived mesenchymal stem cells in acute myocardial infarction: double-blind, randomized controlled trial - BMC Medicine. BMC Medicine. Retrieved November 18, 2023, from https://bmcmedicine.biomedcentral.com/articles/10.1186/s12916-015-0399-z
8. Stem Cell Therapy Safely Repairs Damaged Heart Muscle in Chronic Heart Failure Patients, Study Shows - 11/06/2012.

(n.d.). Johns Hopkins Medicine. Retrieved November 18, 2023, from https://www.hopkinsmedicine.org/news/media/releases/stem_cell_therapy_safely_repairs_damaged_heart_muscle_in_chronic_heart_failure_patients_study_shows

9. Stem Cell Therapy Safely Repairs Damaged Heart Muscle in Chronic Heart Failure Patients, Study Shows - 11/06/2012. (n.d.). Johns Hopkins Medicine. Retrieved November 18, 2023, from https://www.hopkinsmedicine.org/news/media/releases/stem_cell_therapy_safely_repairs_damaged_heart_muscle_in_chronic_heart_failure_patients_study_shows
10. Stem Cell Therapy Safely Repairs Damaged Heart Muscle in Chronic Heart Failure Patients, Study Shows - 11/06/2012. (n.d.). Johns Hopkins Medicine. Retrieved November 18, 2023, from https://www.hopkinsmedicine.org/news/media/releases/stem_cell_therapy_safely_repairs_damaged_heart_muscle_in_chronic_heart_failure_patients_study_shows
11. Sodian, R., Schaefermeier, P., Abegg-Zips, S., Kuebler, W. M., Shakibaei, M., Daebritz, S., Ziegelmueller, J., Schmitz, C., & Reichart, B. (2010). Use of human umbilical cord blood-derived progenitor cells for tissue-engineered heart valves. The Annals of thoracic surgery, 89(3), 819–828. https://doi.org/10.1016/j.athoracsur.2009.11.058
12. Sodian, R., Schaefermeier, P., Abegg-Zips, S., Kuebler, W. M., Shakibaei, M., Daebritz, S., Ziegelmueller, J., Schmitz, C., & Reichart, B. (2010). Use of human umbilical cord blood-derived progenitor cells for tissue-engineered heart valves. The Annals of thoracic surgery, 89(3), 819–828. https://doi.org/10.1016/j.athoracsur.2009.11.058