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USE OF STEM CELL THERAPIES FOR REGENERATION OF DAMAGED HEART TISSUE AFTER ACUTE MYOCARDIAL INFARCTION

Danilo Monteiro Ribeiro
Universidade Anhembi Morumbi (UAM)
Piracicaba - SP
https://orcid.org/0009-0003-7032-8167

Carolina Rapchan Bonilha
Universidade do Oeste Paulista (UNOESTE)
Jaú - SP
https://orcid.org/0009-0003-5492-5025

Marina Marques Vaz de Lima Arjona
Universidade do Oeste Paulista (UNOESTE)
Jaú - SP
https://orcid.org/0000-0002-2432-4427

Nadiny da Silva Florêncio
Universidade Vila Velha (UVV)
Vila Velha - ES
https://orcid.org/0009-0000-6923-3652

Isa Victória Cavalcanti Coelho
Centro Universitário UniFacid
Teresina - PI
https://orcid.org/0009-0004-3290-1193

Aline Barbosa
Universidade de Taubaté (UNITAU)
Taubaté - SP
https://orcid.org/0000-0002-3238-7022

Isadora Pereira Do Nascimento
Universidade Nove de Julho (UNINOVE)
Mauá - SP
https://orcid.org/0009-0004-4647-5324

Caroline Paixão Marques
Universidade Federal de Ouro Preto (UFOP)
Belo Horizonte - MG
https://orcid.org/0000-0002-6613-6643

Géssica Campos Paiva
Centro universitário presidente Antônio Carlos (UNIPAC)
Juiz de Fora - MG
https://orcid.org/0000-0002-4582-7277

João Pedro Rosal Miranda
Centro Universitário UniFacid
Teresina - PI
https://orcid.org/0009-0007-3255-6862

Yasmin Batista Mendes
Centro Universitário do Estado do Pará (CESUPA)
Belém - PA
https://orcid.org/0000-0003-3713-0936

Aloan Carlos Lemos Ferraz
Universidade Iguaçu (UNIG)
Nova Iguaçu - RJ
http://lattes.cnpq.br/6704686068966895

Abstract: Objective: To analyze the current literature on the use of stem cell therapies for the regeneration of injured cardiac tissue after acute myocardial infarction. Methodology: Bibliographic review study through searches in PubMed databases, published from 2017 to 2022, totaling 11 studies used to compose the bibliographic review. Results: The studies demonstrate that different types of stem cells can be used, including embryonic stem cells, induced pluripotent stem cells and skeletal myoblasts. Several mechanisms of action of stem cells occur, including the release of exosomes, the modulation of the inflammatory response, the regulation of gene expression and the interaction with the extracellular matrix. Clinical evidence has shown that stem cell transplantation can result in significant improvements in cardiac function, including increased left ventricular ejection fraction and reduced ventricular volume of muscle and intraventricular cavity. These encouraging results underscore the therapeutic potential of stem cells in regenerating heart tissue and treating cardiovascular disease. Conclusion: It is important to highlight that further studies are needed to deepen the understanding of the mechanisms of action of stem cells and their clinical application, seeking to improve the efficacy and safety of stem cell therapies for heart disease and other medical conditions.
Keywords: Stem cells; Pluripotent stem cells; Skeletal myoblasts.

INTRODUCTION

Despite advances in preventive and curative care in medicine, cardiovascular diseases (CVD) remain the main cause of morbidity and mortality worldwide. It is estimated that CVDs cause about 30% of global mortality and it is expected that 23.6 million people could die from ischemic heart disease and its complications, such as heart failure (HF), by 2030. Coronary artery disease, considered

the main cause of cardiac ischemia, results in the loss of cardiomyocytes, cells that make up the structure of the heart muscle after its prolonged or acute pathophysiological process (MULLER, 2019).

Several studies have sought to prove that stem cells can be used as a promising therapeutic approach in repairing ischemic damage to the myocardium. The use of stem cells in this matter stems from their characteristic of being undifferentiated and their ability to self-renew and give rise to other cell types within the body under appropriate conditions. From improving the cardiac microenvironment to partial regeneration and/or compensation for functional tissue loss and ending with the complete fabrication of a replacement heart, stem cells have raised great hopes (KUMAR et al., 2010).

The ultimate intention is to take advantage of the multifaceted potential of stem cells for effective therapeutic purposes in the treatment of cardiovascular diseases, and the scientific community has been engaged in laborious efforts in recent decades to achieve this goal. Once stem cells are properly propagated, differentiated, and matured, there are several cell delivery method strategies that can be used to deliver them to diseased myocardium, ranging from intravenous administration to direct myocardial injection. However, it is essential to consider several factors related to the graft of transplanted cells and integration, such as the functional contribution to the host myocardium, the electromechanical coupling between the graft and the host organs, and the long-term survival of the cells (SAMAK; HINKEL, 2019). In this context, the objective of this literature review is to analyze the current literature on the use of stem cell therapies for the regeneration of damaged cardiac tissue after acute myocardial infarction.

METHODOLOGY

This is a bibliographic review developed according to the criteria of the PVO strategy, an acronym that represents: population or research problem, variables and outcome. The research was developed based on the following guiding question: "In patients with senile cardiac amyloidosis, what are the emerging therapeutic options and the most effective treatments in reducing disease progression and improving quality of life?". In this sense, according to the parameters mentioned above, the population or problem of this research refers to patients with senile cardiac amyloidosis, with the objective of identifying emerging therapeutic options and more effective treatments to reduce the progression of the disease and improve the quality of life. patients' lives. The searches were carried out through searches in the PubMed and SciELO databases. The descriptors were used in combination with the Boolean term "AND": amyloidosis, cardiac, aged, therapeutics and quality of life. Inclusion criteria were: articles in English, Portuguese and Spanish, published from 2017 to 2022, which addressed the themes proposed for this research, review studies and cohort studies, available in full. Exclusion criteria were: duplicate articles, available in summary form, which did not directly address the studied proposal and which did not meet the other inclusion criteria. After associating the descriptors used in the searched databases, a total of 297 articles were found. Of these, 266 articles belonged to the PubMed database and 31 articles to Scielo. After applying the inclusion and exclusion criteria, 16 articles were selected from the PubMed database and 5 articles from Scielo, totaling 11 studies used to compose the bibliographic review.

RESULTS

MECHANISMS OF ACTION OF STEM CELLS

According to Braga (2020), embryonic stem cells have unique cell cycle activities, as well as microRNAs and proteins, which play a crucial role in survival and differentiation responses after a myocardial infarction. These cells also release exosomes that stimulate the proliferation of cardiac progenitor cells (CPCs) and endogenous cardiomyocytes. The results of this study demonstrate that the administration of exosomes derived from stem cells resulted in significant improvements in the physiological and anatomical processes of cardiac tissue repair, indicating the activation of intrinsic mechanisms involved in exosome-mediated cardiac repair.

It is known that the heart is a post-mitotic organ, with reduced capacity for self-renewal. However, this knowledge has been renewed in the current medical-scientific context. Self-renewing c-Kit cells have been identified that can differentiate into different cell types to promote cardiac regeneration. Embryonic stem cells (ESCs) are an option because of their ability to differentiate into different cell lineages. Despite advances in the induction of ESC differentiation into cardiomyocytes, there are still challenges in obtaining pure and mature populations of these cells (MÜLLER et al., 2018).

Müller et al. (2018), perform extensive research that is currently being conducted on the potential of stem cells at various stages of development for cardiovascular regeneration. Among the types studied, skeletal myoblasts stand out for their ease of recovery in autologous muscle biopsies, rapid proliferation in laboratory cultures, tolerance to hypoxia and ability to differentiate into muscle cells. In addition, they have a low risk of tumorigenesis.

Induced pluripotent stem cells (iPSCs) have been investigated, but their safety has been a concern due to their ability to induce an immune response. To circumvent this risk, new protocols are emerging that use non-integrative methods, such as modified proteins, mRNAs and miRNAs, and even small chemical molecules to minimize the occurrence of mutations during the reprogramming process (MÜLLER et al., 2018).

Another important mechanism in this context is the extracellular matrix (ECM), which is secreted by epicardial cells derived from human embryonic stem cells. This ECM contains high concentrations of fibronectin, which plays a crucial role in heart regeneration in animal models. Previous studies have shown that coordinated secretion of fibronectin, collagen, and growth factors such as epidermal growth factor by fetal fibroblasts stimulate cardiomyocyte proliferation. Therefore, the matrix formed by epicardial cells derived from human embryonic stem cells may contain developmental signals that are absent in the mature post-infarction myocardium, providing a favorable environment even under adverse conditions (MADIGAN & ATOUI, 2018).

The repair process of damaged tissues takes place through direct and indirect/paracrine mechanisms. In the direct mechanism, the transplanted stem cells differentiate into cardiomyocytes or endothelial cells and integrate into cardiac tissue to replace the lost cells. Furthermore, adult and progenitor stem cells can acquire cardiovascular properties through transdifferentiation and cell fusion. The role of paracrine signaling is critical for the beneficial effects of stem cells on the surrounding cardiovascular tissue, as they secrete biologically active molecules that promote cardiac tissue regeneration (MÜLLER et al., 2018).

Paracrine and anti-apoptotic mechanisms are commonly recognized as the main mechanisms of cardiac repair mediated by mesenchymal stem cells (MSCs). In addition to these mechanisms, it is believed that the immunomodulatory properties of mesenchymal stem cells also play an important role in reducing myocardial inflammation and preventing ventricular remodeling after acute myocardial infarction. Studies have shown that MSCs influence the differentiation of B cells into several subclasses and impair the ability of B cells to induce migration to specific proteins such as CXCL12 and CXCL13 (GŸONGYÖSI et al., 2018).

There is the possibility of another mechanism related to the negative feedback loop, in which pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), stimulate MSCs to secrete a protein called gene 6 stimulated by TNF-α (TSG-6). TSG-6 modulates the inflammatory response by redirecting NF-κB transcription factor signaling in resident macrophages, resulting in reduced inflammation and cardiac fibrosis. In addition, prostaglandin E2 (PGE2) is produced when mesenchymal stem cells are activated by molecules such as lipopolysaccharide, TNF-α, nitric oxide, and molecules associated with tissue damage. PGE2 influences the immune response by converting macrophages into an anti-inflammatory phenotype that secretes interleukin-10 (IL-10), a cytokine with anti-inflammatory properties (GŸONGYÖSI et al., 2018).

Regarding the use of skeletal myoblasts, their use is considered in addition to self-renewing c-Kit cells. These cells have advantages such as easy accessibility through autologous muscle biopsies, resistance to ischemic conditions, and low risk of tumorigenicity. Preclinical studies have also shown that skeletal myoblasts can differentiate into muscle structures called myotubules. This differentiation has shown promise, as it reduces the formation of scar tissue within the heart, attenuates changes in the architecture of the cardiac chambers, and improves cardiac function. The positive results of these studies were readily translated into non-randomized clinical trials and demonstrated benefits, such as increased left ventricular ejection fraction (LVEF), improved New York Heart Association (NYHA) functional classification, and improved segmental wall of the heart (MÜLLER et al., 2018).

In this context, personalized medicine plays an important role, as it allows targeted treatment based on the individual characteristics of each patient. Achieving this goal requires determining specific response levels based on individual patient characteristics and identifying specific biomarkers through molecular diagnostics such as blood and plasma profiles. Recent advances in high-throughput sequencing technology, such as RNA-seq, have made it possible to obtain detailed information about patients and their response to stem cell therapy. RNA sequencing allows us to study the expression of thousands of genes simultaneously, providing a comprehensive view of the biological networks involved in pathological and physiological processes (Guo et al., 2020).

According to Madigan and Atoui (2018), epicardial cells derived from human embryonic stem cells (hESC) are a promising tool for advancing regenerative cardiovascular medicine strategies, including cell transplantation and tissue engineering strategies. However, future studies are needed to deepen the understanding of the mechanisms by which epicardial cells propagate the observed benefits and to examine their function in models closer to clinical use. These additional studies are essential for the development of effective

regenerative therapies for heart disease.

Guo et al. (2020), when comparing the gene expression profiles of responders and non-responders to stem cell therapy, it is possible to identify different molecular signatures that can predict the individual response. These signatures may include genes involved in the regulation of inflammation, tissue repair, angiogenesis and other processes relevant to therapeutic efficacy. Classifying patients as responders or non-responders based on their genetic profile allows for a more individualized and targeted approach to stem cell therapy, resulting in higher treatment success rates.

CLINICAL EVIDENCE

A study by Rabiei et al. (2021) showed that the group of patients treated with stem cell transplantation therapy had a significant impact on the increase in left ventricular ejection fraction (LVEF), as well as an important reduction in left ventricular end-diastolic volume (LVEDV) and in left ventricular end-systolic volume (LVETV) compared to the control group. Furthermore, it was found that the improvement in these parameters is obtained approximately 3 months after the patient with AMI has received stem cell therapy. This suggests that this therapeutic measure is clinically relevant and may become a new solution in the treatment of AMI. On the other hand, Lalu et al. (2018) observed a large variation in the results between the analyzed studies and found that the use of stem cells showed relative safety. However, despite having shown a significant improvement in LVEF, some studies have not shown a beneficial effect in reducing mortality. Regarding the safety of this therapy, no significant association was observed between the use of MSCs and the appearance of general adverse effects.

The study involving human mesenchymal stem cells and human induced pluripotent stem cells together showed amplification of cardiac repair in rats with acute myocardial infarction. The research pointed out that human induced pluripotent stem cells, administered intramyocardially, contributed to the rejuvenation of the myocardium and vessels after the ischemic event and were capable of restoring cardiac function, while human mesenchymal stem cells implanted in the epicardium acted together in vascular regeneration through the release of angiogenic paracrine factors in hearts affected by myocardial infarction. It was found that through the paracrine secretion of cytokines and growth factors, mesenchymal stem cells helped to preserve injured cardiomyocytes, allowing the cells to become more resistant to the hostile microenvironment in ischemic tissues. The therapy provided mainly pro-angiogenic, anti-inflammatory, anti-fibrotic and cardiomyocyte maturation effects. The mesenchymal, through the secretion of paracrine factors, improved the retention, distribution and maturation of pluripotent stem cells, responsible for the improvement of cardiac function and regeneration of myocardial cells. However, echocardiography results showed that mesenchymal cells alone did not improve cardiac function in hearts with myocardial infarction. This shows that, despite helping vascular regeneration, they are not sufficient to improve cardiac function and require additional sources of cells to assist in this process (SAMAK & HINKEL, 2019).

With regard to the relationship between exosomes and acute myocardial infarction, a recent study found that the use of exosomes derived from mouse embryonic stem cells stimulates the proliferation of cardiac progenitor cells and myocardial repair through the multiplication of cardiomyocytes. The exosome therapy improved the left ventricular contractility and function of the heart, helping with the ejection fraction. The

study suggests that stem cell-derived exosomes preserve the myocardium and prevent cardiac remodeling by reducing oxidative stress and activating AKT. Furthermore, exosomes are able to stimulate the migration of endothelial cells and protect the myocardium from ischemic injury. However, the mechanism of myocardial protection by exosomes is still not well understood (BRAGA et al., 2020).

The use of stem cell therapies for cardiac tissue regeneration after an acute myocardial infarction contains challenges in the social ethical aspect, ranging from ethical and religious issues to the difficulty of conducting studies capable of effectively assessing the risks and benefits in human beings. Current randomized clinical trials and meta-analyses of acute myocardial infarction demand sufficient statistical data to detect clinically relevant outcomes, but the mean number of participants is less than 50, which has led to inconsistent findings reported in different clinical trials and their previous meta-analyses, which followed for short time intervals, resulting in premature termination of the study and inconclusive results (GŸONGYÖSI M. et al., 2018).

The existence of several gaps in knowledge is evident due to inconsistent or not very comprehensive reports on quality of life and details of the performance of cardiac function. Furthermore, the studies do not describe the cellular potency before the administration of MSCs, nor the characterization of the cellular products used (LALU M. M. et al., 2018). One of the main challenges in therapy using stem cell sheets is limited perfusion, especially in thick cell sheets. In this context, vascularization between leaves and cardiac tissues developed in hearts created with three-dimensional technology and host hearts has shown promise, but requires further research and clinical trials (GUO R. et al., 2020).

CONCLUSION

The mechanisms of action of stem cells have been extensively studied to better understand their capacity for tissue regeneration. Stem cell mechanisms of action involve both direct mechanisms, in which stem cells differentiate into specific cells and integrate into damaged tissue, and indirect/paracrine mechanisms, in which stem cells secrete biologically active molecules that promote cell regeneration. tissue regeneration. Studies have shown that embryonic stem cells possess unique cell cycle activities, as well as microRNAs and proteins, which play a crucial role in survival and differentiation after a myocardial infarction. Preclinical studies have shown benefits in regenerating cardiac tissue, including reducing scar tissue formation and improving cardiac function. However, it is important to highlight that further studies are needed to deepen the understanding of the mechanisms of action of stem cells and their clinical application. Research continues to advance in this area, seeking to improve the effectiveness and safety of stem cell therapies for heart disease and other medical conditions.

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