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Advances In Stem Cell Therapy for Cardiovascular Diseases

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ABSTRACT

Cardiovascular diseases (CVDs) are a major global health concern, but current treatment methods mostly aim at alleviating symptoms rather than repairing damaged heart tissue. It has been suggested that stem cell therapy might be a viable regenerative option for restoring cardiac function by direct differentiation, paracrine signaling, immunomodulation, and angiogenesis. Mesenchymal stem cells (MSCs), cardiac stem cells (CSCs), and induced pluripotent stem cells (iPSCs) have therapeutic potential, according to preclinical study. Biomaterial scaffolding and improved delivery methods also lead to improved cell survival, retention, and integration. Although the outcomes are encouraging, shortcomings associated with this approach include low long-term engraftment, immune rejection, tumorigenicity, and inconsistency in outcomes, which discourage clinical translation. Current studies that have aimed to address these limitations through improved cell selection, combination therapy, biomaterials engineering, and personalized therapies, promise to overcome these obstacles and provide the community with the possibility to transform cardiovascular care beyond palliative care to actual myocardial regeneration.

Key Words:

Cardiovascular Diseases, Stem Cell Therapy, Mesenchymal Stem Cells, Cardiac Stem Cells, Induced Pluripotent Stem Cells, Cardiac Regeneration, Paracrine Signalling, Biomaterial Scaffolds

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1. INTRODUCTION

The cardiovascular diseases (CVDs) are the primary cause of morbidity and mortality on the globe with a crucial socio economic and healthcare burden. The traditional therapies, such as

the pharmacological therapy, lifestyle changes, and surgical approaches are mainly aimed at the symptom management and the elimination of the further disease development instead of the repair of the destroyed cardiac tissue[1]. The natural failure of the adult human heart to replace lost cardiomyocytes once injured, including myocardial infarction, has led to a wide range of studies on the regenerative approach as an alternative. Among them is stem cell treatment, which has shown itself as a transformational therapy, (which) not only restores damaged myocardium, but also restores cardiac function through neovascularization, immunomodulation, and direct differentiation into cardiac cell types.

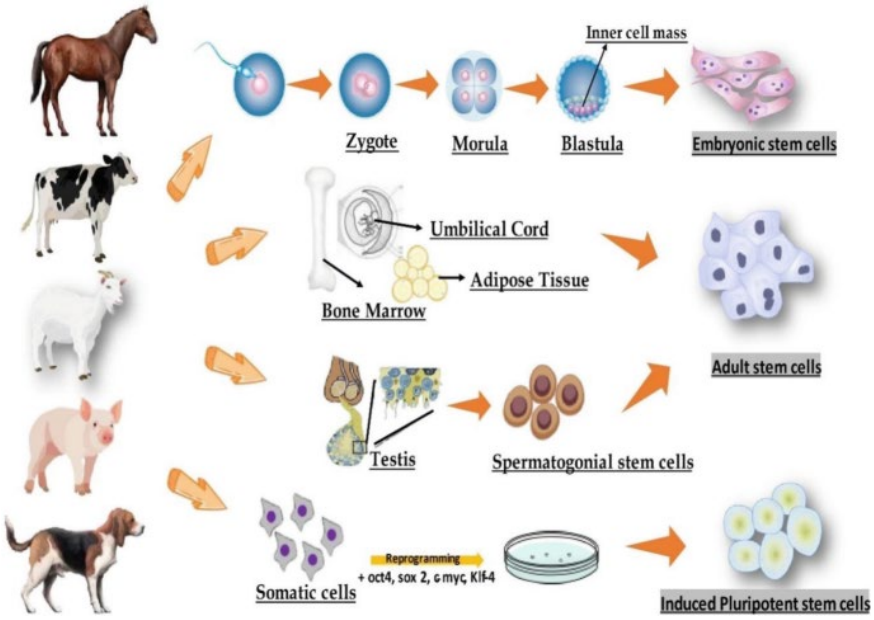

Figure 1: Stem Cell Therapy[2].

The field of regenerative medicine and stem cell biology has grown rapidly in recent years, allowing researchers to investigate a variety of stem cells with various regeneration characteristics. These cells include cardiac stem cells (CSCs), induced pluripotent stem cells (iPSCs), and mesenchymal stem cells (MSCs). Improvements in cell integration, survival, and retention in the host myocardium have been achieved by the combined use of cell transport methods, biomaterial scaffolds, and tissue engineering[3]. In order to address current clinical issues, this review aims to summarize what is known about stem cells' therapeutic potential for cardiovascular repair, assess the mechanisms that contribute to their effectiveness, and discuss recent advances in the field. These advances are important to understand as they promise to change the paradigm in shifting the palliative treatment towards actual cardiac regeneration, which eventually leads to the better outcomes of the patients and lessens the burden of cardiovascular diseases worldwide.

1.1. Background Information and Context

Cardiovascular diseases (CVDs) afflict millions of individuals every year, making them a major contributor to healthcare costs and a leading cause of death worldwide. The traditional approaches to treating heart disease mainly focus on symptom management and disease prevention rather than restoring damaged heart tissue. These methods encompass pharmacological interventions, lifestyle changes, and surgery, among others[4]. However, a new development in regenerative medicine called stem cell therapy shows promise for restoring

damaged cardiac tissue. The therapy approach incorporates many techniques, such as stem cell direct differentiation into vascular and cardiomyocyte cells, paracrine signalling that encourages angiogenesis and tissue regeneration, and immunomodulatory properties that suppress inflammation and fibrosis. In addition to lowering cardiac performance, stem cell therapy may improve long-term patient outcomes and quality of life by resolving the heart's fundamental anatomical and functional abnormalities, thereby transforming the way cardiovascular disease is treated.

1.2. Objectives of the Review

This review aims to:

- To evaluate the therapeutic potential of different stem cell types (MSCs, CSCs, and iPSCs) in cardiac repair, including their regenerative and paracrine mechanisms.
- To analyze the preclinical evidence and outcomes of stem cell therapy on myocardial function, infarct size reduction, angiogenesis, and tissue regeneration.
- To examine the impact of delivery methods and biomaterials (intracoronary, intramyocardial, intravenous, hydrogels, scaffolds) on stem cell survival, retention, and integration in the myocardium.
- To identify mechanisms of action underlying cardiac repair, including direct differentiation, paracrine signaling, immunomodulation, and angiogenesis.
- To highlight translational challenges, gaps, and future research directions for optimizing stem cell therapy for safe, effective, and personalized clinical applications in cardiovascular diseases.

1.3. Importance of the Topic

The area of stem cell-based regenerative approaches is of the highest priority in the framework of cardiovascular medicine since it promises a prospective way to create the intervention that would not be limited to the symptomatic treatment of cardiovascular diseases but also significantly repair and regenerate the damaged tissues of the heart[5]. One of the leading causes of death worldwide is cardiovascular disease, and the available treatments often provide insufficient tools to restore myocardial function that has been lost or prevent long-term consequences. Researchers are working to develop treatments that can restore cardiac infarction and improve functional recovery by utilizing stem cells' regenerative potential, which includes cardiomyocyte-like differentiation, angiogenesis, inflammatory regulation, and reparative paracrine secretion. The development of these therapies can help transform clinical management, decrease hospitalization rates, reduce healthcare expenses, and bring about a greater reduction in morbidity and mortality rates related to cardiovascular conditions, which will provide patients with a better and lasting cure regarding heart disease.

2. CARDIAC STEM CELL THERAPY: PRECLINICAL EVIDENCE, METHODOLOGIES, AND TRANSLATIONAL CHALLENGES

In preclinical models, cardiac stem cell therapy has shown a lot of promise with the studies indicating an improvement in left ventricular function, a smaller size of the infarct, and even an increased level of angiogenesis, especially in MSCs, iPSCs, and cardiac progenitor cell-based systems[6]. To mediate these effects, there is both direct tissue integration and paracrine

signaling. The use of different delivery methods, i.e. intracoronary, intramyocardial, and intravenous, and biomaterial scaffolds have been investigated to maximize cell retention, cell survival, and functional recovery, which is measured through imaging and histological techniques.

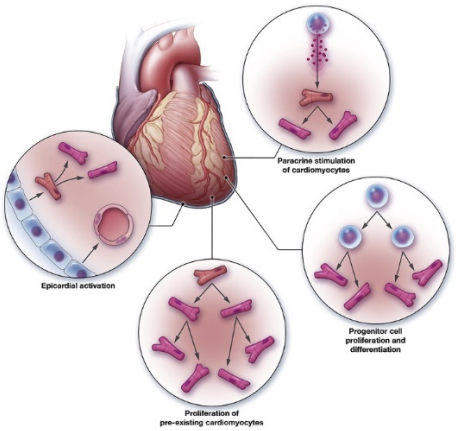

Figure 2: Cardiac Stem Cell Therapy[7].

2.1. Key Research Studies

According to a meta-analysis of research conducted on big animals, cardiac stem cell therapy significantly increased the left ventricular ejection fraction (LVEF) by 10.7%. This finding underscores the enormous potential of stem cells in the repair of myocardial tissue injuries (Nature)[8]. One of the several stem cell types that have been researched is MSCs. Surgery MSCs have been shown to increase the total heart rates, stimulate angiogenesis, and reduce myocardial infarction in the swine and rabbit models of myocardial infarction. These cells seem to have an impact via both direct differentiation into heart tissue and the activation of paracrine signalling mechanisms that promote angiogenesis and tissue regeneration (Nature).

With the ability to differentiate into functional cardiomyocytes and endothelial cells, iPSCs provide yet another intriguing avenue. Transplanting iPSC-derived cells into animal models has shown that they may develop both physically and functionally inside the host heart tissue, improving myocardial functioning and contractility (MDPI)[9]. Furthermore, cardiac progenitor cells and other lineage-specific stem cells have potential, which emphasizes the extent of therapeutic approach that may be achieved. Together these studies highlight the diverse mechanisms in which cell replacement, paracrine signaling, and tissue remodeling can be employed to help cardiac regeneration with the help of stem cell therapy.

2.2. Methodologies and Findings

Various administration strategies have been studied in the administration of cardiac stem cell therapy and each of them has different benefits and drawbacks. Intracoronary delivery enables local delivery of cells to coronary vessels, which can be used in cell homing to ischemic areas, although cell washing could be a constraint[10]. Direct cell delivery to the injured myocardium by intramyocardial injection provides a more efficient method of myocardial engagement with higher local engraftment rates, but less invasive methods such as intravenous injection have shown less effective cardiac retention of delivered cells because of cell entrapment in non-target organs. The efficiency of engraftment, tissue retention, and functional recovery is highly

dependent on the type of delivery method to be used, making it essential to have more streamlined protocols to be used depending on the situation a particular clinical environment.

In an effort to boost survival and integration of cells, scientists have engaged scaffolds, biomaterial support such as hydrogels and extra-cellular matrix-based constructs. These afford support and contribute to cell adhesion, and can be designed to release growth factors, which makes them microenvironmental in a way that supports differentiation and repair of tissues[11]. Post-therapy functional improvements are normally measured with the use of echocardiography to measure parameters including LVEF, fractional shortening and ventricular volumes and histological and molecular measurements to measure cellular integration, tissue re-modelling, angiogenesis and inflammation. Other sophisticated imaging methods, including MRI and PET have been used in preclinical models to provide non-invasive measurement of cell engraftment and myocardial function.

2.3. Strengths and Weaknesses

The therapy of the cardiac stem cells is a promising therapy that can facilitate the repair of tissue and enhance the functionality of the heart using various cell types and novel methods of delivery[12]. Nevertheless, issues such as low long-term engraftment, inconsistent results, immune risks and insufficient clinical optimizations are barriers to its humanization.

- **Strengths:** Due to its ability to promote tissue regeneration and improved functional results in preclinical models, cardiac stem cell treatment has maintained its high therapeutic promise. Because many kinds of stem cells, including cardiac progenitor cells, iPSCs, and MSCs, are present, there are numerous modes of action and treatment methods accessible[13]. The utilization of biomaterial scaffolds and other advancements in delivery methods, such as intracoronary and intramyocardial approaches, have significantly improved the cells' integration, survival, and retention at the site of damage. Additional mechanistic information on preclinical studies shows both direct and paracrine effects of transplanted cells, which can be used to develop more efficacious cardiac therapies.
- **Weaknesses:** Although the cardiac stem cell therapy shows promising preclinical findings, there are a number of limitations associated with it. Sustainable engraftment and structural incorporation of transplanted cells are also not fully developed to prevent the limited ability to extend the life of cardiac repair. The results even within animal models, laboratories, and experimental conditions do not always yield the same results, and hence the reproducibility and standardization are difficult[14]. The translation of these achievements into human clinical trials is also complicated by the problems of immune compatibility, the possibility of arrhythmia or tumorigenicity, and the necessity of the production of cells in large quantities. In addition, the full picture of optimal cell dosage, administration timings, and patient-specific considerations is not fulfilled yet, which indicates the need to conduct more research that would enhance clinical guidelines.

3. CELL-BASED THERAPIES AND DELIVERY APPROACHES FOR CARDIAC REPAIR

Each of the MSCs, CSCs, and iPSCs has a distinct benefit in terms of cardiac regenerative therapy. MSCs reduce inflammation, enhance neovascularization, regulate the

microenvironment via paracrine signaling, and are immunomodulatory, which is appropriate to allogeneic transplantation[15]. CSCs are direct cardiac regenerators of endothelial cells and cardiomyocytes, and combined with MSCs exhibit a cardiogenic synergistic repair effect, but tumorigenicity and differentiation activity are issues. The mode of delivery, such as intracoronary, intramyocardial, and intravenous, biomaterials, such as hydrogels and scaffolds, that enhance cell retention, survival, integration, and vascularization are also useful in successful therapy that provides an optimal microenvironment to repair and restore functionality to myocardia.

3.1. Mesenchymal Stem Cells (MSCs)

It is observed that mesenchymal stem cells (MSCs) have received significant attention in cardiac regenerative medicine because of their extensive therapeutic capability. MSCs can uniformly reduce inflammatory reactions, stimulate neovascularization, and enhance the functioning of the heart following myocardial injury in preclinical models (animated) (Nature). These regenerative properties are credited to their differentiation capacity as well as their capacity to release a wide range of paracrine factors that modify the surrounding tissue[16]. MSCs decrease fibrosis, restrain cell death and improve the recovery and survival of native cardiomyocytes, in general, by modulating the local microenvironment, which assists in promoting overall myocardial recovery.

In addition to its regenerative and paracrine potential, MSCs have important immunomodulatory effects, thereby rendering it especially fit to be used in allogeneic transplantation. They are able to escape immunogenicity and decrease the likelihood of graft rejection and can expand clinical use without there being a rigid matching of donor and recipient[17]. Moreover, MSCs have the ability to migrate to the location of injury and engage with the native cardiac cells, which offer them a structural support as well as biochemical stimulus that promotes tissue repair. All these features can make MSCs a more effective and efficient tool in heart treatment, which is a potential method of enhancing the results of patients with heart disease.

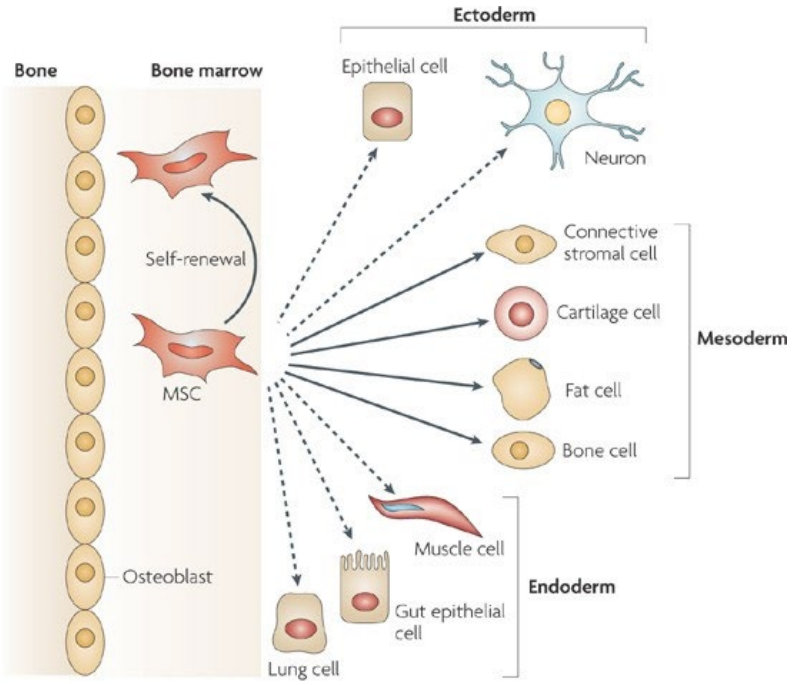

Figure 3: Mesenchymal stem cells (MSCs)[18].

3.2. Cardiac Stem Cells (CSCs)

The cardiac stem cell (CSCs) is a group of resident progenitor cells of the heart which have an innate regenerative capacity of the hurt myocardial tissue. CSCs have also shown the ability to develop into functional cardiomyocytes and endothelial cells in preclinical trials involving large animal models and directly contribute to myocardial repair and to neovascularization (Nature). CSCs assist in the structural and functional repair of the heart after injury by replacing lost or damaged cells of the heart[19]. Their inherent regenerative capacity is what makes them the most appealing choice of targeted cardiac therapy, in particular with such conditions like myocardial infarction where tissue damage is substantial.

CSCs have demonstrated superior functionality in combination with other types of stem cells like MSCs in addition to their standalone therapeutic potential. Combination therapies build upon the synergistic capabilities of the various cells- MSCs secrete paracrine signaling, immunomodulation, as well as anti-fibrotic capabilities, whereas CSCs can regenerate cardiomyocytes directly and form vascular networks[20]. This synergistic response increases tissue repair, enhances cardiac output and can break limitations witnessed in the use of one type of stem cell alone. These combined strategies emphasize the significance of learning cell-specific functions and maximizing stem cell-based strategies to achieve success in the clinical translation of cardiac regenerative medicine.

3.3. Induced Pluripotent Stem Cells (iPSCs)

A recent development in regenerative medicine is induced pluripotent stem cells (iPSC), which provide cardiac treatment (MDPI) an almost limitless source of patient-specific cells. Integrative pluripotent stem cells (iPSCs) are produced by reprogramming adult somatic cells to a pluripotent state. These cells have the ability to develop into many cell types seen in the heart, such as endothelial cells, cardiomyocytes, and smooth muscle cells[21]. The use of iPSCs is particularly appropriate in the context of personalized treatments because of this capability, which makes it possible to replace damaged cardiac tissue with a lower risk of immunological rejection. Premedical research has demonstrated that the iPSC-derived cardiomyocytes have the ability to be incorporated into the host cardiac tissue, enhance the contractile activity, and help form new vessels, which points to their role in cardiac injury repair.

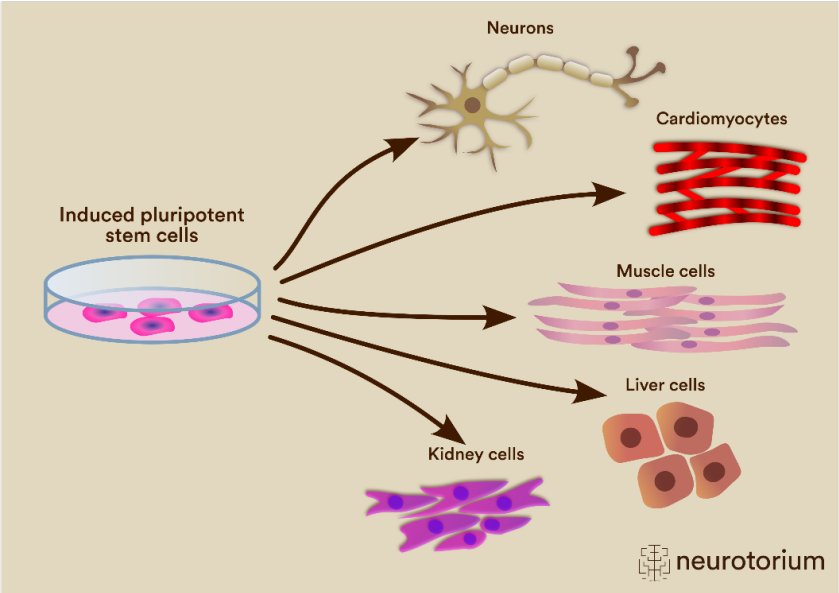

Figure 4: Induced pluripotent stem cells (iPSCs)[22].

However, there are a number of major challenges to the clinical use of iPSCs despite their promise. Among the key issues is tumorigenicity because undifferentiated iPSCs that remain after transplantation can form teratomas. Also, the process of the differentiation needs to be very efficient and strictly controlled in order to generate pure populations of functional cardiac cells, which is still technically challenging[23]. Current studies are underway to come up with safer reprogramming options, more efficient differentiation regimes, and effective control of quality in order to address these dangers. Overcoming these problems is the key to the successful transfer of the therapeutic capabilities of iPSCs in experimental protocols to practical and efficient clinical implementation of cardiac regenerative medicine.

3.4. Delivery Methods and Biomaterials

The kind of cell employed and the distribution method have both been linked to the efficacy of stem cell treatment in mending cardiac tissues[24]. Due to their poor retention, short survival, and inadequate grafting at the trauma site, conventional techniques including intracoronary, intramyocardial, and intravenous administration are often restricted. Current research has focused on better delivery methods that enhance transplanted cell survival and localization in order to get over these challenges. These steps increase the likelihood of a successful recovery and significant tissue regeneration by enabling stem cells to enter and remain in the injured myocardium.

Biomaterial-based techniques including hydrogels, scaffolds, and extracellular matrix mimics have also improved the therapeutic potential of stem cell therapies. These materials provide mechanical stress prevention (protection) and structural support, creating a favorable milieu that promotes vascularization, differentiation, and integration[25]. To further enhance tissue healing, biomaterials may be engineered to provide growth factors or other signaling molecules in a regulated manner. In a bid to increase cell retention, enhance cardiac functionality and simplify the application of preclinical discoveries into effective clinical treatments, researchers are trying to streamline the delivery methodology, as well as, the support biomaterial.

4. MECHANISMS OF ACTION OF STEM CELLS IN CARDIAC REPAIR

Stem cells play a part in heart healing via a variety of interconnected mechanisms, including immunomodulation, paracrine signaling, direct cellular replacement, and angiogenic stimulation. One of the most important is the stem cells' ability to differentiate into cardiomyocytes, smooth muscle cells, and endothelial cells, which allows the injured or destroyed cardiac tissue to be replaced[26]. This direct cellular integration may improve cardiac structure, assist regenerate functional heart tissue, and restore contractile activity. Evidently, it has been shown that cardiac stem cells (CSCs) and iPSC-transformed cardiomyocytes may engraft into injured myocardium, make useful connections with host cells, and directly aid in contraction synchronization, all of which increase cardiac output.

The influence of the stem cells extends beyond direct differentiation via paracrine signaling. In particular, MSCs produce a wide range of bioactive substances that impact the local microenvironment, including as growth factors, cytokines, chemokines, and exosomes. These paracrine signals are able to suppress apoptosis of resident cardiomyocytes, orchestrate extracellular matrix remodeling, reduce fibrosis and attract endogenous progenitor cells to an injured location[27]. These paracrine actions indirectly facilitate tissue repair through stem cells, even in the instances that long term engraftment of transplanted cells is restricted.

The other important mechanism through which stem cells promote the healing of the heart is through immunomodulation. MSCs, as well as some progenitor cells, are also able to regulate the immune response, which lowers the excessive inflammation that is usually seen to worsen myocardial damages following infarction[28]. Stem cells contribute to the establishment of a more favorable environment to promote tissue regeneration and prevent the survival of cardiomyocytes damaged by the immune system due to anti-inflammatory pathways and inhibition of pro-inflammatory cytokines, respectively.

The restoration of perfusion to the myocardium's ischemic regions depends on angiogenesis and neovascularization, both of which are significantly influenced by stem cells[29]. MSCs and CSCs release angiogenic substances, such as vascular endothelial growth factor (VEGF), which promote the formation of new blood vessels and improve the transport of nutrients and oxygen to the wounded tissue[30]. In addition to being linked to transplanted cell survival and integration, improved vascularization also promotes the regeneration of self-generated cardiac tissue, which leads to a sustained improvement in cardiac function.

Table 1: Summary of Key Studies on Stem Cell and Epigenetic-Based Therapies in Cardiovascular Disease

Author(s)	Study	Focus Area	Methodology	Key Findings
Prasad et al. (2020)[31]	Promise of autologous CD34+ stem/progenitor cell therapy for treatment of cardiovascular disease	Autologous CD34+ stem/progenitor cell therapy in cardiovascular disease	Preclinical and clinical studies; transplantation of autologous CD34+ cells	CD34+ cells enhanced neovascularization, improved myocardial perfusion, supported cardiac repair; improved cardiac function in patients with refractory angina and ischemic cardiomyopathy; approach was feasible and safe

Qin et al. (2020)[32]	Role of m6A RNA methylation in cardiovascular disease	Epigenetic regulation of cardiovascular disease via m6A RNA methylation	Molecular and cellular analysis of gene expression patterns associated with cardiac dysfunction	m6A modification regulates genes involved in cardiac hypertrophy, fibrosis, and heart failure; aberrant RNA methylation contributes to disease pathogenesis; targeting m6A regulators may provide therapeutic potential
Rajabzadeh, Fathi, & Farahzadi (2019)[33]	Stem cell-based regenerative medicine	Stem cell therapy for tissue repair and regeneration	Literature review of stem cell types (ESCs, iPSCs, MSCs) and regenerative applications	Highlighted therapeutic potential of stem cells; discussed challenges like immune rejection, tumorigenicity, and limited survival in translating therapy from bench to bedside
Saeedi, Halabian, & Fooladi (2019)[34]	A revealing review of mesenchymal stem cells therapy, clinical perspectives and modification strategies	Mesenchymal stem cell (MSC) therapy for cardiovascular repair	Literature review and analysis of preclinical and clinical studies	MSCs have immunomodulatory, anti-inflammatory, and regenerative properties; strategies like genetic modification, preconditioning, and biomaterials improve cell survival, homing, and therapeutic outcomes
Shi et al. (2022)[35]	Epigenetic regulation in cardiovascular disease: mechanisms and advances in clinical trials	Epigenetic modifications in cardiovascular disease	Review of molecular mechanisms and clinical trials targeting epigenetic pathways	DNA methylation, histone modifications, and non-coding RNAs regulate cardiovascular pathophysiology; epigenetic-targeted therapies may complement conventional treatments and enhance cardiac repair

5. DISCUSSION

The use of stem cell therapy has become a revolutionary approach in cardiovascular medicine with the objective of overcoming the symptom containment to actual myocardial healing. Preclinical evidence shows that various types of stem cells (MSCs, CSCs and iPSCs) can enhance the heart by various pathways, including direct cardiomyocyte-like differentiation, paracrine signaling, immunomodulation and angiogenesis[36]. Further developments in delivery procedures and biomaterial scaffolds have increased cell viability, retention, and incorporation into injured myocardium, with a great deal of potential to be translated to translational scale.

Nevertheless, even though preclinical outcomes are positive, it is clear that numerous issues need to be resolved in order to achieve full clinical applicability of these therapies.

5.1. Interpretation and Analysis of Findings

Neovascularization, reparative factor release, and inflammation modulation are three mechanisms by which MSCs are implicated in heart repair. CSCs give direct tissue repair, and iPSC-derived cardiomyocytes have the potential of patient-specific therapy and eventual personalised medicine. Combination therapies with the complementary capabilities of various types of stem cells seem to improve the efficacy, and the need to optimize cell selection and interactions[37]. It has been shown that both biological and technical factors determine the success of therapeutic delivery since strategies of delivery and biomaterials are critical in enhancing engraftment and functional outcomes.

5.2. Implications and Significance

These results highlight the possibilities of stem cell therapy to transform the cardiovascular care through re-forming myocardial structure and functionality, leading to a smaller infarction, and enhancing the work of the left ventricle[38]. Provided that they are translated to clinical practice effectively, these interventions may help to decrease morbidity and mortality, decrease the cost of healthcare, and increase the quality of life of patients with heart disease. In addition, the knowledge of the mechanisms of the stem cell-mediated repair can offer a useful insight into the cardiac regeneration, and can be used to create the supplementary therapeutic options, including the transgenic cells or the biomaterials-facilitated administration.

5.3. Gaps and Future Research Directions

Although there are encouraging outcomes, there are still a number of gaps. The ability to engage the transplanted cells on a long-term basis and achieve functional integration is limited and the inconsistency of outcomes of studies disrupts reproducibility and clinical standardization[39]. Of current concern are tumorigenicity, immune rejection, and optimum dosing schemes and especially to iPSCs. Further studies ought to be done on:

- Designing more efficient and safer cell reprogramming and differentiation protocols.
- Exploring combination therapies and bioengineered biomaterials to boost cell retention and cell integration.
- Implementing the large-scale clinical trials with proper designs to develop the standard protocols and assess the long-term safety and efficacy.
- Considering individual patient factors, e.g. comorbidities and genetic history, to tailor treatment and enhance outcome[40].

In order to transform stem cell treatments for cardiovascular disorders into effective and feasible therapeutic interventions, these concerns must be addressed.

6. CONCLUSION

Stem cell therapy has great promise as a novel approach to the treatment of cardiovascular diseases; it may one day be able to replace actual myocardial regeneration with symptomatic treatment. Several kinds of stem cells have shown potential to enhance cardiac function in preclinical studies. These include mesenchymal stem cells, cardiac stem cells, induced pluripotent stem cells, and angiogenesis, paracrine, direct differentiation, and immunomodulation. The survival, retention, and integration of the cells have been enhanced by better delivery systems and biomaterial scaffoldings, which will further support functional recovery. Still, the main barriers to clinical translation remain tumorigenicity, immunological inconsistencies, long-term engagement limitations, and unexpected outcomes. Achieving the full therapeutic potential of stem cell-based treatments will depend critically on overcoming these limitations with the aid of improved cell selection techniques, combination therapies, biomaterial design, personalized medicine, and appropriate clinical research. Long-term, further research and advancements in the field might improve patient outcomes, alter the way cardiovascular care is provided, and lessen the prevalence of heart disease worldwide.

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