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Regenerative strategies for myocardial infarction: Integrating cell therapy and scaffold design

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Abstract

One of the most common causes of death in the world is myocardial infarction (MI), and its standard treatment fails to renew the injured cardiac tissue completely. Regenerative medicine has also emerged as a promising avenue for myocardial restoration, with stem cell therapy, scaffold engineering, and cell-seeded biomaterials showing potential in preliminary investigations and initial clinical practice. This paper will explore the various restorative options for MI repair, specifically stem cells, including mesenchymal stem cells (MSCs), induced pluripotent stem cells (iPSCs), and cardiac progenitor cells (CPCs), as well as their applications in conjunction with the use of biomaterial scaffolds. Vital stem cell therapies have been shown to exhibit their paracrine effects, promote angiogenesis, and directly differentiate into cardiomyocytes. Additionally, scaffold designs such as bioactive scaffolds and 3D bioprinting enhance cell survival and promote their incorporation into the infarcted myocardium. The shortcomings, including poor cell engraftment, lack of immunological response, tumor growth, and a lack of long-term safety, are critically evaluated in this review. However, there is also the potential breakthrough of stem cells combined with scaffolds. Lastly, the paper projects future avenues in myocardial regeneration, such as the use of gene-editing tools, personalized medicine, and wearable biosensors with the ability to monitor in real-time. Overall, regenerative therapies hold great promise for improving myocardial function and restoring heart tissue, but clinical translation remains a significant hurdle.

Keywords: Myocardial Infarction; Regenerative Medicine; Stem Cell Therapy; Scaffold Designs; Tissue Regeneration

1. Introduction

The problem of Myocardial Infarction (MI) is still one of the most prevalent causes of death in the world, and its consequences on the level of both a single patient and the entire health system are devastating. It occurs as a consequence of the sudden occlusion of one of the coronary arteries, which causes ischemia and the irreversible damage of the myocardium. Although recent developments in the management of MI have utilized pharmacologic therapies, thrombolytic therapy, and revascularization methods (in the forms of PCI and CABG), these strategies primarily address symptom correction and further damage prevention. Although they have significantly lowered the rates of early deaths, these interventions cannot replenish the structural integrity and the working capacity of the myocardium. In most cases, the end product is progressive heart failure, and this has remained a significant burden on healthcare systems of various nations, with post-MI heart failure accounting for millions of deaths annually (Velagaleti et al., 2008; Roger et al., 2012).

It has been more urgent that damaged myocardium be regenerated to normal so that the heart can behave normally again. Infarction leads to myocardial damage, which cannot be reversed by traditional treatments, and long-term survival is compromised because scar tissue that is not functional takes over the place of the myocardium. The above-mentioned gradual deterioration in cardiac performance is evidence of the inefficiency of old techniques and the necessity to develop innovative solutions. In the past decade, the concept of regenerative medicine has been introduced,

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which has immense potential for restoring myocardial function through tissue regeneration, cell survival, and scar reduction. The most popular ones are cell-based therapies, which have been utilized in preliminary and small-scale clinical trials, with an emphasis on stem cells and biomaterial scaffolds due to their promising behavior (Liew et al., 2020; Wernly et al., 2019).

One of the most promising parts of regenerative therapies is stem cell treatment and myocardial repair. In preclinical models, MSCs, induced pluripotent stem cells (iPSCs), and cardiac progenitor cells (CPCs) have been featured in order to promote regeneration of myocardium through the augmentation of direct myocardial differentiation, secretion of paracrine factors, and augmentation of angiogenesis (Zhang et al., 2024; Makkar et al., 2012). Although the therapeutic potential of stem cells, in terms of disease curing, is well-documented in the literature, their prospects of being cured by or through stem cells have been, and continue to be, impeded by poor engraftment of the stem cells, immune rejection, and the development of tumors. The existence of such barriers to success makes it evident that improvements in delivery, optimization of immunomodulatory strategies, and stability of cells within a hostile environment should be demanded, e.g., in the heart during infarction (Liew et al., 2020; Feric and Radisic, 2016). In addition to stem cells, biomaterial scaffolds are a powerful component in enhancing myocardial repair. Scaffolds are also used as a guide to assist in the growth of transplanted cells, allowing new tissue to develop.

More complex scaffolding strategies, such as 3D bioprinting or the creation of electrically conductive scaffold materials, are expected better to resemble the endogenous extracellular matrix (ECM) and lead to successful functional integration between the grafted cells and the host cardiac tissue (Robles-Loaiza et al., 2022). The interplay between cell-based therapies and biomaterial scaffolds is a combined strategy, where the combination provides a greater effect compared to either method alone, and this could address the disadvantages associated with the application of either cell-based therapies or biomaterial scaffold-based therapies. The combination has shown promise in preclinical studies and has yielded better results regarding tissue regeneration, vascularization, and functional recovery (Sharma et al., 2021).

A major challenge arises clinically, as there has been monumental progress in this field, but a significant stumbling block to real-life application and usage. Concerns regarding long-term safety, immune compatibility, and carcinogenicity persist, which is why preclinical and clinical studies are essential. The existing trends in cardiac regeneration aim to address these challenges and pave the way for future technological approaches, including gene editing and personalized medicine, as well as biosensors incorporated into wearable devices (Polonchuk et al., 2021; Chen et al., 2022). This paper aims to discuss the opportunities of stem cell-based therapy combined with biomaterial scaffolds for treating myocardial infarction. It is also crucial to analyze and examine the existing limitations and barriers that the treatment faces, as well as potential future developments in regenerative cardiac medicine.

2. Methodology

2.1. Research Approach

The type of research design used to critically synthesize the possibilities presented by the combination of stem cell therapies and biomaterial scaffolds in the treatment of myocardial infarction (MI) is the so-called qualitative research design that this paper has taken up as its research methodology. Extensive literature research will consist of the study plan, where scaffold-based strategies, as well as increasing applications of cell-based therapies, have been primarily focused upon. This review will assess the efficacy, safety, and potential drawbacks of the subsequent categories of therapy in myocardial regeneration. The given paper is suitable for using the qualitative method, as it will enable drawing in-depth conclusions about the state of research, revealing more salient themes, and bringing together the results of many preclinical studies, clinical trials, and new technologies.

2.2. Data Collection

The present review article is based on a thorough literature search on peer-reviewed journals, clinical trials, and meta-analyses. Academic tracking of data was carried out by systematically searching information in databases such as PubMed, Google Scholar, and ScienceDirect, which are recognized sources of the information at hand. The relevant articles were identified using the following keywords: stem cell therapy, mesenchymal stem cells, induced pluripotent stem cells, cardiac progenitor cells, biomaterial scaffolds, cardiac regeneration, and myocardial infarction repair. It limited its studies to 20 years to ensure coverage of emerging trends in the profession. To further supplement the search, even clinical trials register data banks, such as ClinicalTrials.gov, were used to identify ongoing and completed clinical trials of stem cell therapy and scaffold-based treatment of MI.

2.3. Inclusion and Exclusion Criteria

A list of inclusion and exclusion criteria was used to state that the studies added to this paper are of good quality and topical. The articles that formed part of the review should have explicitly discussed myocardial infarction and myocardial regeneration, and addressed the issue of applying stem cells or biomaterial scaffolds, either pre-clinically or clinically. The articles focusing on other organs, diseases, or therapies that were not published in peer-reviewed journals and those written in languages other than English were omitted. This step was to ensure that the analysis incorporated only scientifically valid and highly quality studies.

2.4. Data Analysis

A thematic synthesis technique was employed for data analysis after identifying the relevant literature. Using this method helped identify similarities in all the available literature regarding the use of various types of stem cells, scaffold materials, and combination therapies. The initial section of the analysis focused on the sources of stem cells used in MI repair, including mesenchymal stem cells (MSCs), induced pluripotent stem cells (iPSCs), and cardiac progenitor cells (CPCs). Other. The remaining stem cell sources observed included embryonic stem cells (ESCs) and neonatal cardiomyocytes. The review evaluated their capability in producing functional cardiomyocytes, in inducing new blood vessel growth and liberating paracrine factors to mediate tissue repair and regeneration.

The pros and cons of each of these stem cells were examined and compared, as well as their usefulness in clinical applications. This was the second theme, which was subject to analysis regarding biomaterial scaffolds in cardiac regeneration. The necessity of scaffolds is due to the fact that they provide support to the transplanted cells and create an environment conducive to tissue growth and recovery. The scaffolds of various forms have been reviewed, including natural biomaterials, such as collagen and fibrin, and synthetic materials, e.g., PEG and PLGA. The different characteristics of such scaffolds, including their ability to mimic the native extracellular matrix (ECM) and facilitate cell adhesion and tissue integration, were explored. The analysis also incorporated more innovative technology techniques, such as scaffolding using 3D bioprinting and electrically conductive materials, which aim to achieve functional integration and minimize the risk of arrhythmias.

The third theme of the paper on cardiac regeneration focused on the combination of stem cells and scaffolds. Experimental studies have also shown that a combination of the two methods yields a synergistic effect, leading to improved cell survival, retention, and differentiation within an infarcted heart. This part presents a review of both preclinical and clinical studies involving a combination of stem cells and scaffolds, with a focus on the contribution of these combinatory therapeutics to enhancing vascularization, tissue integration, and overall functional restoration. The cons of combination therapy were also addressed in the analysis, including issues such as engraftment, immune rejection, and tumorigenicity.

3. Results

3.1. Global Burden Myocardial Infarction

Despite a global decline in MI mortality, it is still the leading cause of death (Moraes-Silva et al., 2017). The prevalence of heart failure following MI, however, is still horrendously high (Velayati et al., 2008). HF secondary to MI still accounts for a lot of morbidity and mortality (Yves Juilliard et al., 2012) (Lewis et al., 2003). In the United States alone, 6 million individuals are estimated to have HF, cause more than 300,000 deaths annually, and cost the healthcare system around $40 billion (Roger et al., 2012).

Myocardial infarction (MI) imposes enormous economic burdens. In 2010, there were about 1.1 million MI hospitalizations in the United States with a direct healthcare cost of $450 billion (Weintraub et al., 2011). Physical decline- muscle weakness, is a major complication of cardiovascular disease that is frequently seen in older patients. Frailty frequently appears as unintentional weight loss, chronic fatigue, decreased mobility, and physical activity (Fried et al., 2001). Other independent risk factors for MI such as obesity, physical inactivity, hypertriglyceridemia, and elevated inflammatory markers such as high-sensitivity C-reactive protein (hs-CRP) also have strong associations with insulin resistance (Zarich et al., 2006). Numerous studies have confirmed that major cardiovascular risk factors such as diabetes, dyslipidemia, obesity, and smoking are increasing (Puymirat, 2012) (Chockalingam et al., 2006) (Chooi et al., 2019) (Vähätalo et al., 2019). Notably, smoking has been recognized as a useful risk factor for close to 80% of MI events in patients under 55 years (Marques-Vidal et al., 2001).

3.2. Limitations of Conventional Treatments

Despite advances in acute coronary care, traditional therapies for myocardial infarction (MI) such as pharmacologic therapy, thrombolytic therapy, percutaneous coronary intervention (PCI), and coronary artery bypass grafting (CABG) are primarily focused on the restoration of perfusion and limitation of ischemic damage. These interventions improve survival and diminish early mortality but cannot reverse the irreversible injury to viable cardiomyocytes and the following remodeling of the cardiac tissue. The injured tissue is increasingly substituted by fibrotic scar tissue lacking the contractile strength required for effective cardiac output. Surprisingly, none of the present treatments can restore the structural derangement or reconstitute the necrotic myocardium. Naturally, this remodeling will ultimately result in ventricular dilatation, reduced systolic function, and eventually heart failure. Beta-blockers, ACE inhibitors, and statins can dampen some of these effects but cannot restore the mechanical and electrical properties of the native myocardial. Thus, the majority of MI survivors experience progressive loss of cardiac function and continue to be at risk for recurrent events, arrhythmias, and sudden cardiac death. (Liew et al., 2020)

Other than that, there is also an ongoing issue of long-term outcomes. With successful revascularization and adequate medication, over 30% of MI patients become chronic heart failure within five years (Sharma et al., 2021). This clearly depicts the biological constraints of current practices and highlights the need for new therapies that go beyond short-term stabilization. Social and economic costs are also involved. MI and its consequences are costing the US health care system billions of dollars annually, such as readmission, device implantation, and end-stage heart failure management (Wernly et al., 2019). The cost will continue to grow as populations age and risk factors for cardiovascular disease grow.

3.3. Need for Regenerative Strategies

Despite these constraints, there is tremendous enthusiasm towards regenerative medicine as a therapeutic modality for cardiac repair. Regenerative therapies differ because they aim to restore the immune function and tissue integrity, as opposed to inhibiting further damage, as is the case with traditional medications. These efforts are aimed at transplanting new, healthy cardiomyocytes into the infarcted myocardium, enhancing vascularization, and restructuring the post-MI environment to facilitate healing. One of the leaders of this area is stem cell therapy. Mesenchymal stem cells (MSCs), due to their immune-modulatory properties and the simplicity of their collection, have been extensively researched in both pre-clinical and phase 1 clinical trials. The process of direct differentiation into cardiomyocytes is not standard, and MSCs have a strong paracrine effect, as they release growth factors and cytokines that induce angiogenesis, inhibit apoptosis, and regulate inflammation (Liew et al., 2020; Wernly et al., 2019).

The second prospective option is that of induced pluripotent stem cells (iPSCs), which can be reprogrammed using adult somatic cells and differentiated into cardiomyocyte-like cells. These give a theoretically unrestricted source material of patient-specific cells and reduce the risk of immunological rejection. Existing research has demonstrated that iPSC-based cardiac patches can physically and functionally integrate into host tissue, restoring contractile function and diminishing infarct size in animal models (Zhang et al., 2024). At the same time, biomaterial scaffolds are designed to promote survival, retention, and integration of transplanted cells. Hydrogel, electroconductive material, or biodegradable polymer cardiac patches can possibly replicate the extracellular matrix, mechanical support, and even electrical signal transmission to synchronize the contraction (Sharma et al., 2021). Stem cell-seeded scaffolds are a versatile platform for cellular and mechanical repair.

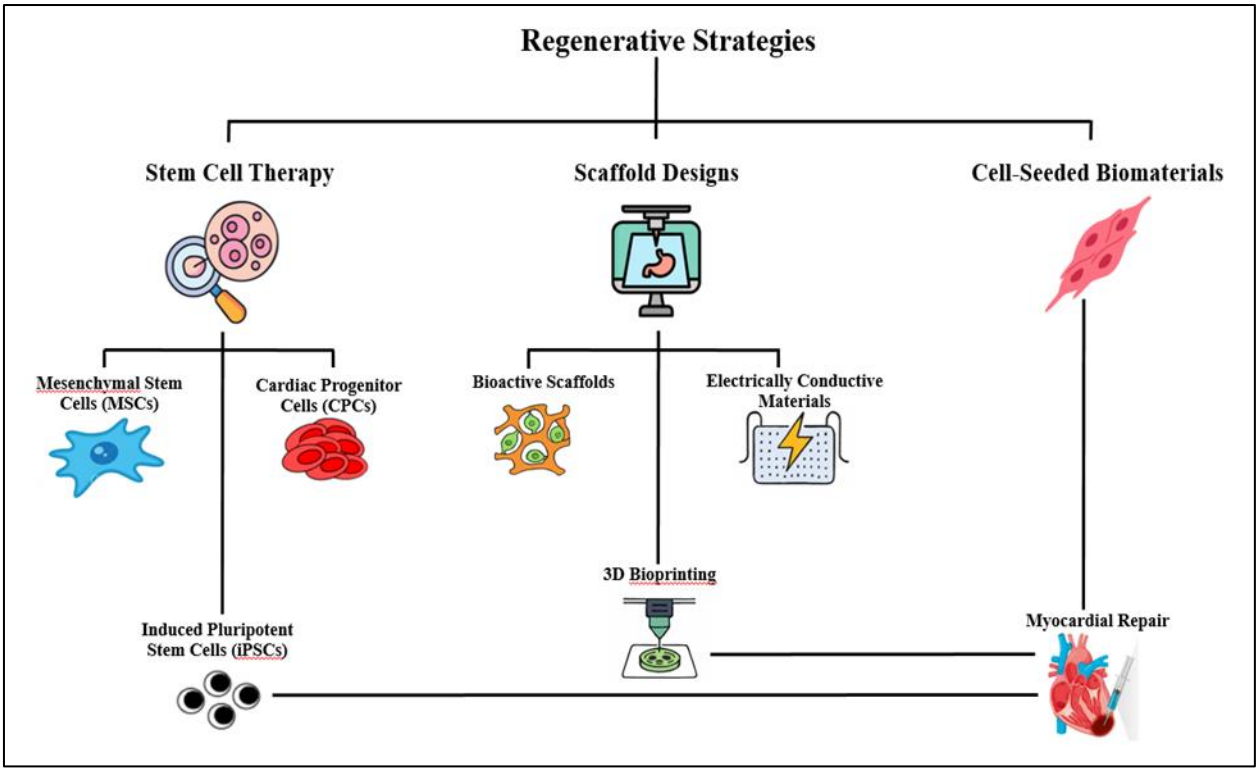

Figure 1 Flowchart illustrating various regenerative strategies for tissue repair (image generated through biorender)

Unexpectedly, when the combination of scaffolds and cells is being used, it is providing better results than when either one is applied alone. In preclinical models, biomimetic scaffolds seeded with MSCs or iPSCs provided better results than control groups in terms of vascular density, fibrosis, and functional recovery (Ferric and Radisic, 2016). While such developments hold great promise, clinical translation remains an issue. Cell survival, arrhythmogenicity, immunogenicity, and long-term safety are all significant barriers to overcome. Yet, the progress of the last decade in regenerative cardiology offers a firm platform for future therapeutics that will not only save lives but also restore heart function at the cellular level. Figure 1 shows flowchart illustrating various regenerative strategies for tissue repair, including stem cell therapies, scaffold designs, and cell-seeded biomaterials, with myocardial repair as one of the key outcomes.

3.4. Cardiac Injury and Repair Biology

Myocardial infarction (MI) has a chain of biological reactions that change the function and morphology of the heart fundamentally. The disease process is begun when a coronary artery is blocked, typically by a breach of atherosclerotic plaque, leading to lack of oxygen and nutrition supply to a segment of the myocardium. In a few minutes, the ischemic area undergoes permanent damage, and necrosis and apoptosis lead to death of the cardiomyocyte quickly (Herial et al., 2014). Despite the central location of the heart, mammalian adult cardiomyocytes possess very limited regeneration capacity. Unlike other tissues, there is low cardiomyocyte turnover in the adult, typically less than 1% per year. This gradual rate of replacement is largely because adult cardiac cells exit the cell cycle shortly after birth and enter the post-mitotic state (Bergmann et al., 2009). Thus, at an infarct, when cells are lost, the myocardium cannot be replaced normally.

When the heart is injured, it undergoes a tightly regulated healing process with three overlapping phases: inflammation, proliferation, and remodeling. Resident immune cells like neutrophils and monocytes first migrate into the infarcted tissue and remove necrotic debris with the simultaneous release of pro-inflammatory cytokines like TNF-α and IL-6. This inflammatory response is needed for healing but also has the potential to further damage adjacent viable tissue (Koreth et al., 2016). In the proliferative phase, myofibroblasts and fibroblasts take over the microenvironment, secreting extracellular matrix (ECM) proteins, which contribute to scar formation. Sadly, though the fibrotic matrix maintains the mechanical strength of the ventricular wall, it is non-conductive and lacks the contractile function of native cardiomyocytes. The rigid, non-conductive scar, over a period of time, impairs electrical communication and leads to adverse ventricular remodeling further impairing heart function (Talman and Ruskoaho, 2016).

These post-infarction changes can persist in secret, leading to cardiac failure if the original infarction was large or treatment was late. Indeed, studies have shown that fibrosis and inflammation extend more than just the acute phase, providing a chronically inhospitable milieu for tissue repair (Malliaras and Marban, 2011). This biological limitation is the reason why merely improving blood supply through revascularization is not enough to remediate cardiac damage—it retards progression but fails to recover lost function. Emerging evidence suggests that techniques targeted at modifying the immune response, increasing cardiomyocyte proliferation, or adding regenerative cells and scaffolds can affect the course of cardiac repair. However, these therapies must act in tandem with the complex healing process to avoid upsetting the delicate balance of inflammation and remodeling (Sutton and Sharpe, 2000).

3.5. Cell-Based Therapy in Myocardial Repair

Since the adult heart possesses very little regenerative capacity, scientists are exploring cell-based treatments to substitute injured cardiomyocytes and restore myocardial function. Stem and progenitor cells have become the hope of the last two decades as potential agents for the regeneration of the heart. These approaches focus not only on cell replacement, but also on optimizing the local environment for healing through paracrine effects and immunomodulation.

3.5.1. Mesenchymal Stem Cells (MSC)

Mesenchymal stem cells (MSCs), classically derived from bone marrow, adipose tissue, or the umbilical cord, have been in the limelight because they are easy to harvest, low in immunogenicity, and abundant in paracrine activity. While MSCs do not necessarily differentiate into cardiomyocytes in vivo, they secrete a range of bioactive molecules, including growth factors, cytokines, and exosomes, which modulate inflammation, avoid fibrosis, and enhance angiogenesis in the infarct area. Moreover, MSCs possess immunosuppressive properties, which include modulating T-cell growth and suppressing macrophage activation. These characteristics make them highly sought after for application in a clinical environment, where immunological rejection is a major setback (Denton and Gokhale, 2019).

3.5.2. Induced pluripotent stem cells (iPSCs)

Induced pluripotent stem cells (iPSCs) allow the patient-specific cardiomyocytes to be obtained through reprogramming somatic cells. iPSCs might be induced to differentiate into functional cardiomyocytes under the appropriate conditions and are thus a promising cell source for cell replacement therapy. But there are still problems, such as the risk of teratoma development, failure of maturation of cardiomyocytes derived from iPSC, and requirement for controlled integration with host tissue. Due to these limitations, however, iPSC technology is progressing very quickly, and its promise as personalized regenerative medicine still remains (Anguraj Sadanandam et al., 2013).

3.5.3. Cardiac Progenitor Cells (CPC)

Cardiac progenitor cells (CPCs) are c-kit or Sca-1 positive stem cell-like cells that are found everywhere in the heart. They can give rise to cardiomyocytes, endothelial cells, and smooth muscle cells. CPCs have been used in clinical trials such as SCIPIO and CADUCEUS to test their safety and efficacy in patients with ischemic cardiomyopathy. While initial results showed increased heart function and reduced scarring, later studies have raised concerns over the reproducibility and long-term efficacy of such results. Still, CPCs remain a prominent figure in the field, particularly when combined with supportive biomaterials (Makkar et al., 2012).

3.5.4. Delivery Strategies

Successful delivery of therapeutic cells is important in order to realize maximum retention and functional gain. Localized delivery is delivered through direct intramyocardial injection but is invasive, whereas intracoronary infusion provides a less invasive route but with lower retention. New injectable hydrogel systems are also being developed to enhance cell survival, engraftment, and integration by creating a conducive environment upon transplantation. Delivery mode plays a significant role in defining outcomes. Injectable biomaterials, particularly with controlled degradation and bioactivity, may have the potential to fill the gap between cellular therapy and the long-term repair of the heart (Curtis and Cicchetti, 2013).

4. Scaffold-based cardiac regeneration

Use of scaffold-based technologies for the repair of the heart has greatly improved the therapeutic potential of tissue engineering approaches. Scaffolds refer to bioactive matrices that mimic the native ECM and provide structural support and biochemical cues that direct cardiac cell survival, growth, and alignment following myocardial infarction.

4.1. Biomaterials Used

Scaffolds can be formed from natural biomaterials such as collagen, fibrin, and gelatin, which are biocompatible and have high affinity with the physiological ECM. These biomaterials support cell adhesion and remodeling but can lack mechanical strength. Synthetic polymers such as polyethylene glycol (PEG), polylactic acid (PLA), and polylactic-co-glycolic acid (PLGA) can provide highly controlled mechanical properties, degradation rates, and functionalization. But unless digested, they can initiate immunological responses (Aydemir Sezer et al., 2020).

4.2. Hydrogel Systems

Hydrogels are widely used for cardiac devices because they are injectable and possess ECM-like hydration properties. After injection, these materials gel in situ and adapt to the geometry of the infarct region. Smart hydrogels are capable of responding to stimuli such as pH and temperature, and they are designed to release medicinal chemicals or nourish object AtIndexed cells over time.

Recent research also prefers composite hydrogels, which are composed of natural and synthetic components to ensure biocompatibility and material strength, and thus are best suited in targeted cardiac repair (El-Husseiny et al., 2023).

4.3. Electrically Conductive Scaffolding

One of the primary limitations of traditional biomaterials is that they cannot conduct electrical impulses, which are required for coordinated contraction of cardiac muscles. To address this, electroconductive scaffolds were created using electroconductive materials such as polyaniline (PANI), carbon nanotubes (CNTs), and PEDOT: PSS. These substrates facilitate crossing of the electrical gap between native and synthetic myocardium, reduce the risk of arrhythmias, and enhance excitation-contraction coupling (Kaveh Roshan Infar et al., 2024).

4.4. 3D Bioprinting and Cardiac Patch

Three-dimensional bioprinting facilitates accurate construction of cardiac tissue architecture with bioinks comprising living cells and ECM components. Printed scaffolds can be tailored to the patient anatomy and facilitate vascular integration, a critical shortcoming in large tissue repair. Similarly, stem or progenitor cell-based custom cardiac patches are constructed and are in the process of being implanted onto the epicardium for the improvement of cardiac function. Patches represent site-specific regeneration without systemic cell injections, minimizing risk and maximizing treatment specificity (Moraes-Silva et al., 2017). This table compares different stem cell types used for myocardial regeneration, highlighting their origin, differentiation potential, advantages, limitations, and supporting references.

Table 1 Comparison of Various Stem Cell Types for Cardiac Repair

Stem Cell Type	Origin	Differentiation Potential	Advantages	Limitations	References
Mesenchymal Stem Cells (MSCs)	Bone marrow, adipose tissue, umbilical cord	Limited cardiomyocyte differentiation; strong paracrine activity	Easy isolation, low immunogenicity, angiogenesis, anti-apoptotic effects	Low differentiation into cardiomyocytes, short-term engraftment	Liew et al., 2020; Warmly et al., 2019
Induced Pluripotent Stem Cells (iPSCs)	Reprogrammed adult somatic cells (e.g., skin or blood cells)	High differentiation potential into functional cardiomyocytes	Patient-specific, theoretically unlimited source, lowers risk of immune rejection	Tumorigenicity risk, incomplete maturation of cardiomyocytes	Zhang et al., 2024; Anguraj Sadanandam et al., 2013
Cardiac Progenitor Cells (CPCs)	Found in the heart (e.g., c-kit or Sca-1 positive)	Can differentiate into cardiomyocytes, endothelial cells, and smooth muscle cells	Ability to regenerate heart tissue, clinically tested	Concerns over reproducibility and long-term efficacy	Makkar et al., 2012; Liew et al., 2020

Embryonic Stem Cells (ESCs)	Derived from early-stage embryos	Can differentiate into any cell type, including cardiomyocytes	High regenerative potential	Ethical concerns, risk of teratoma formation, immunogenicity	Milliards and Marban, 2011; Kim et al., 2022
Cardiac Stem Cells (CSCs)	Found within the heart	Can differentiate into cardiomyocytes, endothelial cells, and smooth muscle cells	Potential to regenerate the heart tissue, less risk of immune rejection	Limited number, cannot regenerate large infarctions efficiently	Makkar et al., 2012; Liew et al., 2020
Pericytes	Mesodermal cells located on the walls of small blood vessels	Can differentiate into cardiomyocytes and endothelial cells	Strong regenerative capacity, can help form new blood vessels (angiogenesis)	Poor survival rate when transplanted into infarcted tissue	Ferric and Radisic, 2016; Zhang et al., 2024
Neonatal Cardiomyocytes	Newborn heart tissue	Can regenerate cardiac tissue to a certain degree	High regenerative ability, less prone to arrhythmias	Limited availability, ethical concerns around neonatal tissues	Milliards and Marban, 2011; Liew et al., 2020
Tissue-Specific Stem Cells	Derived from tissues like skeletal muscle, liver, and adipose tissue	Limited ability to differentiate into cardiomyocytes but have potential through paracrine signaling	Low immunogenicity, easy to isolate	Limited differentiation potential into cardiomyocytes	Ferric and Radisic, 2016; El-Husseini et al., 2023
Hematopoietic Stem Cells (HSCs)	Bone marrow	Primarily blood cells, with some evidence of differentiation into cardiac tissue	Easy access, potential for regeneration through paracrine effects	Limited cardiac differentiation	Makkar et al., 2012; Warmly et al., 2019

5. Synergistic Strategies: Cell and Scaffold-Based Cardiac Regeneration

While scaffold implants and cell therapies have been promising individually in the repair of the heart following myocardial infarction (MI), their combination has been more effective in overcoming the biological limitations and attaining maximal regenerative benefits.

Through the hybridization of the mechanical and biochemical support of scaffolds and the capability of cellular regeneration, therapeutic benefits are maximized.

5.1. Maximizing Cell Survival and Retention

Low survival of cells and engraftment of the transplanted cells in the ischemia unfavorable environment of the infarcted heart is one of the major challenges to cell-based heart therapy. Because of mechanical washout, inflammation, and lack of anchoring, a significant number of stem cells are lost within hours when administered alone. By physical anchorage, immune shielding against pathologic stimulation, and the facilitation of diffusion of nutrition, scaffolds possess a permissive microenvironment that promotes cell survival. Hydrogels and patch-like matrices have been shown in rodent and porcine models of MI to enhance tissue integration and engraftment rates significantly when co-delivered with mesenchymal or is-derived cardiomyocytes (Sharma et al., 2021).

5.2. Strategies for Immune Tolerance

Apart from this, immune response may be modulated using a combination of cells and scaffolds. Immunomodulatory drugs like interleukin-10 or TGF-β mimetics that help in tissue remodeling and suppression of inflammation may be

incorporated into biomaterials. Allogeneic transplantation rejection can also be minimized by seeding scaffolds with genetically modified hypo-immunogenic cells. Such an immune-tolerant environment supports long-term engraftment and functional incorporation of therapeutic cells, and it is thus possible to avoid the use of immunosuppressive medication (El-Husseini et al., 2023).

5.3. Recuperated Function in Large Animal Models

Large animal models, more closely approximating human physiologic conditions, have demonstrated potential functional improvement using hybrid cell-scaffold constructs. In pigs following myocardial infarction, cardiac patches with implanted stem cells and conductive polymers have been found to have greater myocardial wall thickness, decreased scar area, and greater ejection fraction. Besides that, the evolution in technology in 3D bioprinting has allowed one to achieve the precise cell distribution within the scaffolds for improved electrical contact and vascularization. The preclinical rodent-to-trial translational gap has been bridged to a large degree by the engineered grafts (Robles-Loaiza et al., 2022). This field of cardiac regeneration is progressing toward clinical use by incorporating synthetic biomaterials and physiologically active cells. More integrated tissues, restored function, and long-term safety are required for successful human use, all of which are provided by these systems.

6. Limitations and Challenges

The cell-scaffold combination is very promising for repairing myocardial infarction (MI) but would need some critical concerns to be resolved before it can be regarded as a potential, safe, and effective therapy for patients.

6.1. Efficiency of Engraftment

Most of the implanted cells die or persist in the myocardium for too short a time to have a noticeable effect, a significant limitation. Ischemia, inflammation, mechanical stress, and inadequate metabolic support all result in cell death. Therapeutic effectiveness is diminished because, although scaffolding is used, only a fraction of the cells remains functionally integrated in the long term. Cell survival enhancement through the use of bioactive materials or co-delivery of survival factors is one of the main research areas (Sharma et al., 2021).

6.2. Immunological Barriers

Scaffold material or cell surface marker modifications can induce immune responses even when the cells are autologously derived from the patient. Donor cells (allogeneic transplants) have a greater chance of being rejected. Therapeutic benefit could be balanced against chronic inflammation secondary to an immunological incompatibility or foreign material. Immunomodulatory scaffolds, hypoimmunogenic cells, or transient immunosuppression are methods to minimize such risk (Sharma et al., 2021).

6.3. Issues of Tumorigenicity and Ethics

If there are any remaining undifferentiated cells after transplantation, stem cell sources like iPSCs carry a low but actual risk of untimely proliferation or tumor development. To protect against this, strict cell purification and monitoring methods must be employed. The use of embryonic stem cells is also limited by ethical and legislative issues, though iPSCs reduce these to a certain degree. Cells need to be well described and characterized before they can be applied clinically (El-Husseini et al., 2023).

6.4. Long-Term Effectiveness and Safety

A dearth of longitudinal information regarding cell-scaffold therapy efficacy and safety in humans and large animal models currently exists. Examples of long-term complications include arrhythmias resulting from electrically heterogeneous graft-host interfaces, inflammatory scaffold degradation byproducts, or mechanical mismatches jeopardizing heart function under stress. Promising preclinical results, however, will require stringent clinical trials to define long-term results in a variety of patient populations (Robles-Loaiza et al., 2022).

7. Future Directions in Cardiac Regeneration

Although cardiac repair techniques have advanced considerably in the recent past, novel techniques need to be found for delivering these therapies to the clinic. Biomaterial optimization, cellular function optimization, and individualized therapy are the main areas of new advances in cardiac tissue engineering.

7.1. Bioactive Scaffold Design

Next-generation scaffolds are being engineered to do more than just provide a simple framework. Bioactive scaffolds induce cardiomyocyte proliferation, suppressed inflammation, and promoted vascularization by releasing signal factors such as cytokines and growth factors (e.g., VEGF and IGF-1) in a controlled fashion. Upon demand, these scaffolds can release bioactive signals upon exposure to environmental stimuli such as pH level or enzyme level. To promote healing, a smart, dynamic environment in constant communication with the local tissues is in development (Robles-Loaiza et al., 2022).

7.2. Gene-Edited Stem Cells

Cell therapy is being transformed through the application of CRISPR-Cas9 and other gene-editing tools. Scientists can engineer more effective therapeutic cells by editing mesenchymal stem cells or iPSCs to improve survival, decrease immune recognition, or increase regenerative function. Gene-edited iPSCs, for instance, can be rendered hypoimmunogenic, so that they can be transplanted to groups of patients with no risk of rejection. Cells can also be programmed to secrete therapeutic proteins, increasing their potential for repair after transplantation (Kim et al., 2022).

7.3. Personalized, Patient-Specific Therapies

For regenerative treatments to be as effective as possible, personalization is crucial. Researchers can create disease-specific models and cardiac patches that are tailored to the individual's own genetic and physiological profiles through the use of patient-derived iPSCs. Improved integration, lower risk of rejection, and preclinical evaluation of a patient's likely response to treatment are all facilitated by this approach. Incorporating AI and machine learning into patient information may also contribute to case-by-case selection of the best regenerative method (Liudmila Polonchuk et al., 2021).

7.4. Integration with Wearable Technology and Monitoring

Biosensing scaffolds that constantly monitor local parameters like pH, temperature, or inflammatory responses can be utilized in the therapies of future cardiac regeneration. These scaffolds' ability to communicate with external wearables or applications to monitor healing, identify issues early, and inform therapy adjustment can usher in a new era of smart tissue repair (Chen et al., 2022).

8. Conclusion

Myocardial infarction (MI) is a major global health problem with limited effective approaches to genuine myocardial regeneration. Traditional treatment is largely symptomatic and preventive of further damage but is not effective in the repair of damaged cardiac tissue. Recent advances in the area of regenerative medicine have provided encouraging avenues, utilizing methods such as stem cell therapy, novel scaffolds, and integrative approaches that mimic the complex structural and functional features of native cardiac tissue. Cell therapies involving mesenchymal stem cells, iPSCs, and cardiac progenitors possess tremendous potential to initiate myocardial repair by paracrine signaling, immunosuppression, and direct tissue regeneration. Their therapeutic application has been encumbered by poor engraftment, immunodetection, and restricted long-term survival. Scaffold-based approaches, specifically bioengineered hydrogels and 3D cardiac patches, provide the biomechanical and biochemical signals for better integration and function. When used in combination, these solutions have a synergistic effect and significantly increase therapeutic outcomes.

Even with promising outcomes in preclinical models, tumorigenicity, ethical considerations, and long-term safety need to be addressed with caution. Future developments, like bioactive scaffold systems, gene edited stem cells, and individualized regenerative therapies, will be the game-changer in cardiac treatment. Combining patient-specific iPSC technology and AI-assisted design, and real-time biosensing is bound to open the doors to clinically viable, patient-specific heart repair approaches. Finally, the convergence of tissue engineering, stem cell biology, and sophisticated biomaterials opens a new and revolutionary method for repairing damaged myocardium — a major leap in the fight against heart failure and myocardial infarction complications.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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