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The Role of Stem Cells in Cardiac Tissue Repair After Myocardial Infarction: Physiological Mechanisms

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A B S T R A C T

Introduction: Myocardial infarction induces IRI, leading to cardiomyocyte necrosis, neutrophil-driven inflammation, and fibroblast-mediated fibrosis, culminating in ventricular dysfunction. Stem Cell such as MSCs promote angiogenesis via VEGF/HGF paracrine secretion; CPCs differentiate through Notch/Wnt for tissue replacement; iPSCs enable patient-specific remuscularization with Cx43 integration.

Aim: The purpose of this study is to investigate the role of stem cells in cardiac tissue repair after myocardial infarction via physiological mechanisms.

Discussion: Stem cell–based therapies represent a promising yet evolving approach for cardiac repair following myocardial infarction. Preclinical models consistently demonstrate improvements in angiogenesis, attenuation of fibrosis, and partial restoration of ventricular function; however, these outcomes have not been fully replicated in clinical trials.

Conclusion: This review synthesizes mechanisms for advancing clinical translation. the future of cardiac regenerative medicine lies in the integration of mechanistic insights with bioengineering and molecular innovation.

Keywords: stem cells, heart tissue, Myocardial Infarction, physiological mechanisms

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Introduction

Ischemia-reperfusion injury (IRI) occurs when blood flow is restored to ischemic cardiac tissue, paradoxically exacerbating damage through explosive reactive oxygen species (ROS) production, calcium overload, and mitochondrial permeability transition pore opening, leading to cardiomyocyte necrosis. This triggers an inflammatory cascade with neutrophil infiltration and cytokine release (e.g., TNF-α, IL-6), culminating in fibrosis via fibroblast activation and excessive collagen deposition, which impairs ventricular function(1, 2).

Even after extensive research in the lab and on humans, we still do not fully understand how stem cell-based treatments improve heart function following a heart attack. In some cases, this is still being debated. While initial research focused on direct cardiomyocyte replacement, growing evidence suggests that paracrine signaling, immunomodulation, and extracellular vesicle-mediated communication may play a larger role than myocardial regeneration. Furthermore, the disparity between significant outcomes in animal models and minimal benefits in human clinical trials highlights ongoing challenges in clinical translation, such as poor cell engraftment, limited survival, and safety concerns(3).

This review seeks to critically integrate contemporary evidence regarding the physiological mechanisms that facilitate stem cell-mediated cardiac repair post-myocardial infarction, focusing on paracrine effects, immunoregulatory pathways, microRNA and exosome signaling, as well as novel cell-free and bioengineered approaches. This review aims to elucidate mechanistic controversies and pinpoint essential pathways for enhancing translational efficacy in regenerative cardiology by synthesizing results from preclinical models and clinical trials(4).

Role of Stem Cells in Regeneration

Mesenchymal stem cells (MSCs), derived from bone marrow or adipose tissue, primarily exert paracrine effects through the secretion of VEGF and anti-inflammatory factors (such as IL-10), thereby promoting angiogenesis and diminishing apoptosis in the myocardium following ischemia-reperfusion injury (IRI), rather than engaging in extensive direct differentiation. Cardiac progenitor cells (CPCs), including Sca-1+ or PDGFRα+, are dormant cardiac cells that express markers like c-kit (which is controversial because of contractility issues). They change into cardiomyocytes, endothelial cells, and smooth muscle through Notch/Wnt signaling for targeted regeneration. Induced pluripotent stem cells (iPSCs), derived from adult cells, produce functional cardiomyocytes through Wnt/Notch signaling pathways for engineered patches that integrate with host tissue via Cx43 gap junctions, diminish fibrosis, and enhance ejection fraction. Embryonic stem cells (ESCs) yield significantly but encounter ethical and immunogenic challenges (1).

Stem cells for cardiac regeneration include several key types, each with distinct origins and mechanisms. MSCs primarily support repair through paracrine signaling rather than direct differentiation(5, 6).

Major Types

- Cardiac Progenitor Cells (CPCs): Resident heart cells expressing markers like c-kit or Sca-1, capable of differentiating into cardiomyocytes, endothelial cells, and smooth muscle for targeted regeneration(7).

- Induced Pluripotent Stem Cells (iPSCs): Reprogrammed adult cells that generate functional cardiomyocytes via pathways like Wnt and Notch, ideal for patient-specific therapies(8).

- Embryonic Stem Cells (ESCs): Pluripotent blastocyst-derived cells with high cardiomyocyte yield, though limited by ethical concerns and immunogenicity(8).

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Table 1. Mechanisms by Stem Cell Type.

Stem Cell Type	Primary Mechanisms	Key Pathways/Factors	Outcomes in Repair
Mesenchymal Stem Cells (MSCs)	Paracrine secretion; immunomodulation	VEGF, HGF, SDF-1; exosomes with miR-126; M2 macrophage shift	Angiogenesis; ↓ apoptosis/fibrosis; ↑ EF by 5-10% (9)
Cardiac Progenitor Cells (CPCs, c-kit+)	Direct differentiation; endogenous activation	Notch/Wnt signaling; follistatin release; Ca^{2+} oscillations	Cardiomyocyte replacement; proliferation of host cells (10)
Induced Pluripotent Stem Cells (iPSCs)-derived CMs	Electromechanical integration; remuscularization	Cx43 gap junctions; Tbx5/CRISPR maturation; sarcomere alignment	Scar reduction (20%); restored contractility (11)

Therapeutic Outcomes

In trials, these mechanisms raise ejection fraction by 5 to 10%. In IRI models, exosomes help ROS scavenging and mitochondrial function. Low engraftment (<5%) is a problem that can be solved with preconditioning or biomaterials (11). Stem cell therapies possess transformative potential for cardiac repair; however, they necessitate enhanced mechanistic understanding and clinical translation strategies to surmount enduring obstacles (12).

Expanded Mechanisms

New evidence points to transdifferentiation beyond paracrine dominance, in which MSCs adopt partial cardiomyocyte phenotypes by epigenetic reprogramming, expressing troponin and connexin-43 for limited electromechanical coupling. Tunnelling nanotubes mediate mitochondrial transfer from mesenchymal stem cells to stressed cardiomyocytes rescuing bioenergetics and reducing IRI-induced dysfunction. CPCs secrete Follistatin which inhibits myostatin, promoting cardiomyocyte hypertrophy and proliferation (13) thus activating endogenous repair.

Clinical Trial Insights

Phase II trials like TAC-HFT report modest EF gains (2-4%) with CD34+ cells, attributed to sustained VEGF release rather than myogenesis, confirmed by serial MRI. iPSC patches in porcine MI models achieve 20% scar reduction with aligned sarcomeres, though human scalability lags due to maturation deficits (14)

Advanced Solutions

CRISPR-Cas9 was used to genetically engineer iPSC-CM to overexpress Tbx5, which made them more mature and capable of handling calcium like an adult. Nanofiber scaffolds together deliver cells and SDF-1 gradients, increasing blood vessel density by three-fold. Exosome preconditioning avoids viability issues and miR-126 enriches payloads, reducing apoptosis by 40% (15). In animal models of myocardial infarction stem cells have positive effects on cardiac function, scar size and vascularization mainly through paracrine mechanisms (16).

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Table 2. Summary of Selected Studies.

Stem Cell Type	Animal Model	Key Outcomes	Mechanisms	Reference
Bone Marrow MSCs (BM-MSCs)	Yorkshire pigs (chronic MI)	↑ LVEF by 5-7%; ↓ fibrosis; ↑ vasculogenesis	Paracrine (VEGF, IGF-1); reduced apoptosis	Tompkins (16)
Cardiac Stem Cells (CSCs, c-kit+)	Mice (AMI)	Myocardial regeneration; normalized LV function	Direct differentiation to cardiomyocytes/endothelium	Tompkins (16)
Human iPSC-CMs	Pigs/non-human primates (MI)	20% scar reduction; synchronous integration	Remuscularization; electromechanical coupling	Yuexin (17)
Cord Blood Stem Cells (CBSCs)	Rats (MI)	↑ survival; ↓ LV remodeling; improved EF	Angiogenesis; anti-fibrotic effects	Duran (18)
Mesenchymal Progenitor Cells (MPCs)	Sheep (AMI)	40% ↓ scar size; 50% ↑ vascular density	Paracrine growth factors; endogenous CSC proliferation	Tompkins (16)

microRNA molecules secreted by mesenchymal stem cells and Myocardial Infarction

Mesenchymal stem cells (MSCs) secrete miRNAs primarily via exosomes, exerting cardioprotective effects in myocardial infarction (MI) by modulating apoptosis, inflammation, fibrosis, and angiogenesis(19).

Key MSC-Derived miRNAs in MI

• miR-200b-3p: Targets BCL2L11/NLRP1 to reduce cardiomyocyte apoptosis, infarction size, fibrosis, and inflammation; MSC-exosomes improve EF and limit oxidative stress in MI mice(19).

• miR-182-5p: Inhibits GSDMD-mediated pyroptosis and inflammation in I/R injury, enhancing cardiac function and reducing scar via exosomal delivery (20)

• miR-21-5p, miR-199a: Promote survival and angiogenesis by targeting PTEN; enriched in MSC-exosomes for post-MI repair(21).

• miR-29 family, miR-24: Anti-fibrotic, suppressing collagen deposition and TGF-β pathways(21)

Therapeutic Impact

Exosomes from MSCs that carry these miRNAs work better than whole cells. They cut the size of the infarct area by 20–40%, increase the density of blood vessels, and change macrophages to the M2 phenotype without causing problems with engraftment. When overexpressed, negative regulators like miR-377 make fibrosis worse. These miRNAs are cell-free options for treating MI (22).

miRNAs mediate anti-fibrotic effects post-myocardial infarction (MI) primarily by targeting TGF-β/Smad pathways, collagen synthesis genes, and fibroblast activation markers(23).

Table 3. Key Anti-Fibrotic miRNAs and Targets.

miRNA	Primary Targets	Mechanism in MI Fibrosis	Reference
miR-24	Furin (TGF-β activator), Smad2/3	Inhibits CF differentiation/migration; ↓ collagen-1, α-SMA in infarct border zone	Wang(24)
miR-29 family	Col1A1, Col3A1, Elastin, FBN1	Direct suppression of ECM genes; downstream of TGF-β/Smad3	Maries(23)

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miR-130a (inhibition)	PPARγ	↓ PPARγ restores anti-fibrotic signaling; prevents myofibroblast differentiation	Li(25)
miR-221	cFB activation factors	Enhances CF survival but inhibits profibrotic activation	Zhou (26)
miR-486-5p	SMAD2, Col6α6	↓ fibroblast proliferation/migration; ameliorates fibrosis in animal models	Ji (27)
miR-328 (upregulation)	TGF-β pathway	Reduced in infarct border; anti-fibrotic when restored	Du (28)

Challenges and Limitations

Even though early clinical and preclinical results are promising, there are numerous issues that make stem cell-based therapies for myocardial infarction difficult to implement in many patients.

One of the most serious issues is that cells do not survive or engraft properly. After being injected into the heart muscle or coronary arteries, less than 5-10% of transplanted cells typically survive beyond the first few days. This is due to ischemic microenvironments, oxidative stress, pro-inflammatory cytokines, and mechanical washout. This poor retention significantly reduces the likelihood of long-term myocardial repair, shifting the therapeutic They benefit from short-term repolarization to short-term paracrine capacity(29).

The risk of arrhythmogenesis is particularly high in the case of stem cell-derived cardiomyocytes. Immature electrical phenotypes, action potential heterogeneity, and incomplete electromechanical coupling with the myocardium can predispose to ventricular arrhythmias, a finding that has been demonstrated in various large animal studies using iPSC-derived cardiac grafts(30).

Immunorejection and immunosuppression challenge stem cell therapy. Mesenchymal stem cells are immunocompetent. However, allogeneic or allogeneic administration may elicit immune responses. Embryonic stem cells and products derived from induced pluripotent stem cells (iPSCs) are highly susceptible to immunoincompatibility and require immunosuppressive protocols with long-term safety implications(31).

Tumorigenesis and instability, especially in stem cells, create additional genetics. The remaining unthymized cells, the genomic alterations that occur during reprogramming, or the increased duration of in vitro conditions, increase the theoretical risk of teratoma formation and consequently increase regulatory and safety concerns(32).

There are still challenges in translating the results of animal models into human trials. Rodent and large animal models have shown significant improvements in reducing scarring and cardiac function. However, human clinical trials have generally only involved moderate-to-severe individuals. This translational gap exists because of changes in heart muscle size, immune response, disease duration, and associated health complications(33).

Advanced Solutions

To overcome the limitations of conventional stem cell therapy for MI, many innovative strategies have been developed to improve cell viability, safety and therapeutic efficiency. The goal of these approaches is to improve the biological function of stem cells, improve their delivery and to use cell derived products to prolong cardiac repair.A key approach is to genetically and molecularly pre-condition stem cells to better survive ischaemic stress and inflammatory environments. Genetic modification of cells to produce more cardiogenic and prosurvival factors such as Tbx5, GATA4, VEGF, and Bcl-2 using CRISPR-Cas9 or viral vector has been shown to increase the likelihood of cell survival, electrical maturation and improved function after transplantation (34).

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Another important step is the development of delivery systems supported by biomaterials. Injectable hydrogels, nanofibrous scaffolds, and bioengineered cardiac patches provide mechanical support to the infarcted myocardium while improving cell retention and local delivery of paracrine factors. These platforms decrease mechanical washout, improve angiogenesis and promote coordinated electromechanical coupling between transplanted cells and host tissue Concurrent with this there has been increased interest in cell free regeneration approaches particularly stem cell derived extra cellular vesicles and exosomes.These vesicles contain bioactive proteins, lipids and microRNAs that mirror many of the therapeutic effects of the original stem cells, but with lesser risks of immune rejection, arrhythmogenesis or tumorigenesis. Engineered exosomes carrying cardioprotective microRNAs (miR-126, miR-21 and miR-199a) showed superior effect in decreasing apoptosis, fibrosis and oxidative stress in preclinical models of myocardial infarction (35).

Future Perspectives

In the future, the emphasis of stem cell-based therapies for heart failure appears to be on safety, durability and real efficacy of the graft, rather than simply increasing the number of cells or their differentiation potential. New evidence suggests that the beneficial effects of stem cells are more likely mediated by the secretion of messenger substances (paracrine signalling), and therefore, therapies are moving towards cell-free and engineered approaches. In this scenario, extracellular vesicle and microRNA-based therapies represent a promising option, as they may mimic the positive effects of stem cells but without the risks of transplant failure, immune rejection or even tumorigenesis. For instance, the production of exosomes containing cardioprotective microRNAs such as miR-126, miR-21, and miR-199a might allow for better control of fibrosis, angiogenesis, and survival of heart muscle cells in anaemic tissues (36).

The future of cardiac regenerative therapies will probably be based on genetic and epigenetic engineering. Control of key transcription factors such as Tbx5 and GATA4, and improvement of calcium control in cells through tools such as CRISPR-Cas9, could lead to better maturation and greater stability of iPSC-derived cardiomyocytes, which could ultimately reduce the risk of arrhythmias (37).

On the other hand, biomaterial-based drug delivery systems, such as injectable hydrogels, nanofibrous scaffolds and cardiac patches, can enhance cell survival, provide mechanical support, and enable targeted and timed release of bioactive agents . These approaches are expected to improve electrical and mechanical coordination and sustained repair of damaged cardiac tissue. Finally, future research should address practical issues such as standardisation, the feasibility of large-scale production, and regulatory and legal issues. In order to be successful in the clinic, standardisation of how the cells are made, choosing the right patients to get the therapy and finding biomarkers that can reliably predict whether a patient will respond to the therapy will be essential. In addition, the combination of stem cell-derived products with pharmacological therapies, mechanical heart unloading or rehabilitation programs may improve therapeutic effects. In the coming years, the future of cardiac regenerative therapies is anticipated to evolve from traditional cell transplants to more targeted, mechanism-based, engineered and even cell-free approaches that may better tailor and ensure the safety of treatments for heart attack patients (38).

Conclusion

Stem cell–based therapies represent a promising yet evolving approach for cardiac repair following myocardial infarction. Accumulating evidence from experimental and clinical studies indicates that the beneficial effects of stem cells are driven

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predominantly by paracrine signaling, immunomodulation, and extracellular vesicle–mediated communication, rather than durable cardiomyocyte replacement. While mesenchymal stem cells, cardiac progenitor cells, and pluripotent stem cell–derived cardiomyocytes each exhibit distinct regenerative properties, their translational impact in human studies has thus far remained modest.

Preclinical models consistently demonstrate improvements in angiogenesis, attenuation of fibrosis, and partial restoration of ventricular function; however, these outcomes have not been fully replicated in clinical trials. Key limitations—including poor cell survival and engraftment, arrhythmogenic risk, immune responses, and manufacturing challenges—continue to constrain clinical efficacy and scalability. These discrepancies underscore the need to reconsider traditional paradigms of cell transplantation and to focus on mechanism-driven therapeutic strategies.

Emerging approaches such as cell-free therapies, including stem cell–derived exosomes and microRNA-based interventions, as well as genetic engineering and biomaterial-assisted delivery systems, offer innovative solutions to overcome current barriers. By enhancing safety, precision, and durability, these advanced strategies may bridge the gap between experimental success and clinical translation.

In conclusion, the future of cardiac regenerative medicine lies in the integration of mechanistic insights with bioengineering and molecular innovation. A shift toward personalized, scalable, and cell-free regenerative therapies holds significant potential to improve outcomes for patients with myocardial infarction and to advance the field toward clinically meaningful myocardial repair.

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CRediT authorship contribution statement

Conceptualization, Methodology, Validation, Formal Analysis, Investigation, Resources, Software, Data Curation, Writing–Original Draft Preparation, Writing–Review & Editing, Visualization, Supervision, Project Administration: AP, MK.

Declaration of Generative AI and AI-assisted technologies in the writing process

No AI writing assistance was utilized in the production of this manuscript.

Conflict of interest

The authors have no competing interests to disclose.

Ethical considerations

No human participants, animals, clinical data or personally identifiable information were used in this work. Only previously published literature was used. Therefore, no ethical approval or informed consent was required for this review study according to the research ethics guidelines at institutional and international levels.

Data availability statement

The data that support the findings of this study are available on request.

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