Stem Cell Research & Therapy

REVIEW

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Stem cell therapy for myocardial infarction and atherosclerosis: mechanisms, challenges, and future directions

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Abstract

Myocardial infarction (MI) and atherosclerosis (AS) are the deadliest category of diseases globally. Preliminary clinical and preclinical studies have shown that stem cell therapy can alleviate symptoms; however, it has not yet achieved full functional regeneration of myocardial or vascular tissues. Stem cell therapy has shown the ability to reverse pathological processes through tissue repair, angiogenesis, and immune modulation. The main challenges of clinical translation remain the low survival rate and uncontrolled differentiation after stem cell transplantation. This paper systematically describes the classification, characteristics, and mechanisms of action of stem cells, as well as the pathological features of MI and AS and the limitations of traditional therapy. It discusses the challenges and solutions for the clinical translation of stem cell therapy. Such advances are expected to promote the development of precise, intelligent, and systematic stem cell therapies for MI and AS. This is very useful for creating multidisciplinary innovation systems in the future.

Keywords Myocardial infarction, Atherosclerosis, Stem cell therapy, Embryonic stem cells, Mesenchymal stem cells, Induced pluripotent stem cells, Cardiac stem cells, Regenerative medicine

Introduction

Myocardial infarction (MI) and atherosclerosis (AS) are among the leading causes of death worldwide [1, 2]. According to the World Heart Report 2023, cardiovascular diseases (CVDs) cause approximately 18.6 million deaths each year, accounting for 32% of global mortality [1, 3]. The disease burden is particularly severe in low and middle-income countries [4]. In recent years, significant lifestyle changes have exerted considerable impacts on health outcomes, coinciding with a marked increase in the prevalence of MI and AS. In these regions, uneven distribution of medical resources, limited health awareness, and environmental pollution hinder effective prevention and control. Data indicate that MI and AS-related mortality is about 40% higher in low and middle-income countries than in high-income countries, and this disparity is likely to widen further in the coming decades [5].

Despite the efficacy of contemporary therapeutic interventions, including coronary artery bypass grafting and anticoagulant administration, these approaches fail to restore function in myocardial or vascular tissues, thereby predisposing patients to persistent heart failure risks. For instance, in the context of myocardial infarction, conventional treatments can promptly resolve vessel

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obstruction and preserve viable myocardial tissue. This does not guarantee the complete regeneration of damaged cardiomyocytes, which can result in progressive cardiac dysfunction, frequently culminating in end-stage heart failure. Epidemiological data indicate that approximately 15 million cases of acute myocardial infarction (AMI) occur worldwide each year, of which about 20% of patients will develop heart failure within 5 years after the onset [2]. This situation highlights the limitations of conventional therapies in repairing damaged myocardial tissue.

In recent years, breakthroughs in regenerative medicine have provided a new paradigm for the treatment of CVDs [6]. Stem cell therapy has shown the potential to reverse pathological processes through three mechanisms: tissue repair, angiogenesis, and immune regulation. As a type of cell with self-renewal and multilineage differentiation potential, stem cells have unique advantages in repairing damaged tissues. For example, mesenchymal stem cells (MSCs) have become one of the most widely studied stem cell types in clinical research due to their easy accessibility, low immunogenicity, and strong paracrine functions. Studies have shown that MSCs can significantly promote angiogenesis and tissue repair by secreting exosomes that release bioactive molecules such as vascular endothelial growth factor (VEGF) and hepatocyte growth factor (HGF) [7]. In addition, Induced Pluripotent Stem Cells (iPSCs) also provide new possibilities for the precision treatment of CVDs owing to their high plasticity and potential for personalized therapy [8].

However, low survival rates and uncontrolled differentiation remain major bottlenecks in clinical translation. For example, the survival rate of coronary MSCs is less than 5% within 72 h, which seriously limits the clinical effect of stem cell therapy [9]. In addition, ectopic differentiation and tumorigenic risks remain major challenges. Although iPSCs possess the pluripotent differentiation potential of embryonic stem cells (ESCs), they might differentiate into non-target tissues or even form teratomas after transplantation. These issues pose significant challenges to the clinical translation of stem cell therapy.

Innovations across multiple disciplines have gradually revealed solutions with the potential to overcome existing bottlenecks. For example, researchers can precisely regulate the lineage commitment and functional characteristics of stem cells through the application of gene-editing technologies [10]. CRISPR-Cas9 technology can significantly boost the efficiency of transforming stem cells into cardiomyocytes by knocking out pluripotency genes or activating cardiomyocyte-specific transcription factors. In addition, the integration of biomaterials engineering and tissue engineering provides new ideas for stem cell therapy. The application of smart hydrogel scaffolds and 3D bioprinting technology not only improves the survival rate of stem cells in vivo but also enables the construction of complex heart tissue [11].

In the future, as multidisciplinary research deepens, the prospects for stem cell therapy in MI and AS are expected to improve. Through methods such as technological innovation and interdisciplinary collaboration, it is reasonable to expect that stem cell therapy will soon become a routine and effective treatment, helping more patients with MI and AS regain their health.

Classification of stem cells and their treatments

MSCs secrete paracrine factors such as VEGF and HGF, which promote angiogenesis and ameliorate the ischemic microenvironment [12]. Other paracrine mediators, including stromal cell-derived factor-1α (SDF-1α) and insulin-like growth factor-1 (IGF-1), enhance neovascularization, attenuate cardiomyocyte apoptosis, and promote functional recovery in preclinical models of myocardial infarction. Collectively, these paracrine effects represent a major mechanism underlying the therapeutic potential of MSCs in cardiovascular regeneration.

MSCs can be isolated from bone marrow, adipose tissue, and umbilical cord, and exhibit immunomodulatory, paracrine, and homing properties [13]. The therapeutic effects of MSCs are predominantly mediated by their secretome.

Mesenchymal stem cells (MSCs)

Exosomes derived from MSCs carry microRNAs such as miR-21 and miR-210, which regulate cardiomyocyte apoptosis and fibrosis. In addition, MSCs recruit endogenous progenitor cells to promote angiogenesis through the CCL2/CCR2 axis. Clinical phase Ⅲ trials have confirmed that intravenous infusion of bone marrow MSCs can increase left ventricular ejection fraction (LVEF) by 3.8%, although limitations such as low cell survival (< 10%) and functional heterogeneity remain, as demonstrated in studies such as the TAC-HFT trial [14]. For example, MSCs overexpressing CXCR4 can improve myocardial homing efficiency by 5.2-fold. MSCs are widely present in bone marrow, adipose tissue, and umbilical cord tissue, with multidirectional differentiation ability and immunomodulatory function, making them the main cell source for current clinical trials (Table 1) [15–17].

Induced pluripotent stem cells (iPSCs)

iPSCs acquire pluripotency by reprogramming somatic cells with transcription factors and possess the differentiation potential of ESCs, along with the advantages of autologous transplantation [18]. The key technological breakthroughs include: First, non-integrated vectors can increase reprogramming efficiency to 0.1–1%; second,

Table 1 Reviewing the advantages and limitations of different types of stem cells

Stem cell type	Source	Advantage	Limitation	Action pathways	References
Embryonic stem cell	Intracapsular cell mass (ICM)	High differentiation efficiency (70–85%); Secreting angiogenic factors (such as VEGF, HGF)	Ethical disputes; Tumorigenic risk; Immune rejection	Direct differentiation	[51, 54, 67, 68, 72]
Mesenchymal stem cells	Bone marrow, fat, umbilical cord and other tissues	Strong immune regulation ability; Abundant paracrine function (such as secretion of miR-21, miR-210 and other regulatory factors; Homing characteristics	Cell survival rate after transplantation Low (< 10%); Functional heterogeneity Paracrine effect	Paracrine effect; Homing effect of immune regulation	[15, 16, 63]
Induced pluripotent stem cells	Reprogramming somatic cells by transcription factors	Both the differentiation potential of ESC and the advantages of autologous transplantation; High purity cardiomyocytes can be prepared (95% purity)	Residual reprogramming epigenetic memory might lead to differentiation bias; Tumorigenic risk	Direct differentiation	[6, 21, 77]
Cardiac stem cell	Adult heart	Exosomes can promote cardiac function recovery (such as miR-146a); Can be transplanted directly to the damaged heart	The relevant studies are relatively few, and the mechanism of action needs to be further clarified	Intercellular substance transfer; anti-oxidation; anti-apoptosis; promote angiogenesis	[25, 27, 28]

the directed differentiation system guided by single-cell omics can achieve the preparation of cardiomyocytes with 95% purity [19]. The world's first iPSC-derived myocardial cell sheet transplantation trial conducted in Japan (clinical trial number: jRCT2052190081) showed that 4 of 5 patients with heart failure had significant improvement in myocardial perfusion [20]. However, residual reprogrammed epigenetic memory might lead to differentiation bias. The recently developed machine learning-assisted epigenetic editing technology (EpiCRISPR) can reduce the inter-batch coefficient of variation in gene expression to 6.4% by reprogramming somatic cells with transcription factors [21–23].

Cardiac stem cells (CSCs)

Dendritic cell-derived exosomes (DCexos) can transform skin fibroblasts into active cells, thereby reducing the MI area and improving cardiac function, similar to cardiac sphere-derived cells (CDCs) [24, 25]; After being transplanted directly into the damaged heart, secreted exosomes from the body, particularly miR-146a, are shown to promote regeneration and function. Cardiac progenitor cells (CPCs) in the adult heart, including CDCs, can release exosomes that promote endothelial tube formation, reduce cardiomyocyte apoptosis, block fibrosis, and enhance cardiac function under various circumstances. Human DC exosomes enhance cardiac performance and vessel density, inhibit fibrosis, and reduce infarct size within 7 to 30 days after MI [26–28].

Action pathways of stem cell therapy

The main pathways of stem cell therapy include the paracrine effect, direct differentiation, immune regulation, homing effect, intercellular material transfer, antioxidant and anti-apoptotic effects, and the promotion of angiogenesis [29]. The paracrine effect means that MSCs release VEGF, FGF, and other growth factors through exosomes, which promote the proliferation of vascular endothelial cells and angiogenesis in ischemic areas. Stem cells are capable of secreting a variety of bioactive molecules, including growth factors, cytokines, and chemokines [29]. These factors can promote the repair and regeneration of damaged tissues. For example, MSCs promote angiogenesis and tissue repair by secreting VEGF and HGF [30]. In addition, exosomes secreted by stem cells carry regulatory molecules such as miRNAs, which can regulate cell apoptosis and fibrosis [31]. Direct differentiation means that iPSCs can differentiate into functional cardiomyocytes in a specific microenvironment to repair the infarcted area [32]. Stem cells can also differentiate into functional cells to replace damaged cells within that same specific microenvironment. For example, iPSCs can be differentiated into cardiomyocytes in vivo to repair infarcted myocardial tissue and promote functional recovery of the tissue. Immunomodulation involves the suppression of T cell activation and the reduction of pro-inflammatory factor release, particularly TNF-α and IL-6, by MSCs to alleviate myocardial inflammation. Stem cells have immunomodulatory functions and can reduce inflammatory responses by secreting anti-inflammatory factors and inhibiting the release of pro-inflammatory factors [33].

The homing effect refers to the ability of stem cells to migrate to the site of damaged tissues. For example, MSCs that have been genetically engineered to express the CXCR4 receptor on their surface can significantly improve their homing efficiency in the area of myocardial infarction. Intercellular material transport describes how

stem cells can enhance the function of damaged cells by transferring organelles, such as mitochondria, to these cells through direct cell-to-cell interaction or tunneled nanotubes (TNT). This intercellular material transfer mechanism provides energy support for damaged cells and promotes their survival and functional recovery. Antioxidant and anti-apoptotic effects refer to the ability of stem cells to secrete antioxidant factors, remove reactive oxygen species in the body, and reduce oxidative stress. In addition, anti-apoptotic factors secreted by stem cells can prevent cell death and protect damaged tissues. These effects help maintain tissue homeostasis and promote its repair and regeneration [34].

Disease mechanisms of MI and stem cell therapeutic targets

MI is a leading cause of morbidity and mortality worldwide, characterized by acute ischemic injury and subsequent maladaptive remodeling of the heart. The multifactorial nature of MI pathophysiology provides multiple therapeutic entry points for stem cell–based interventions, which can restore contractile myocardium, modulate inflammatory responses, attenuate fibrosis, and promote angiogenesis. In this section, we summarize the pathological mechanisms of MI and highlight how different stem cell strategies target these processes to improve cardiac repair and functional recovery.

Pathophysiology of MI

MI results from acute coronary artery occlusion that causes severe ischemia and oxygen deprivation, leading to rapid cardiomyocyte loss through necrosis, apoptosis, and newly recognized forms of regulated cell death such as necroptosis and ferroptosis. The release of damage-associated molecular patterns (DAMPs) from dying cells initiates a robust inflammatory cascade characterized by infiltration of neutrophils and monocytes and the release of cytokines such as IL-1β, TNF-α, and IL-6 [35]. While this inflammatory phase is required for clearance of necrotic tissue, excessive activation exacerbates injury and predisposes to maladaptive healing [36]. Subsequently, fibroblasts differentiate into myofibroblasts that deposit extracellular matrix proteins, resulting in scar formation which preserves structural integrity but impairs electromechanical coupling and diastolic compliance. In the chronic stage, adverse ventricular remodeling ensues, with chamber dilation, compensatory hypertrophy of surviving cardiomyocytes, and the development of arrhythmogenic substrates. These processes collectively lead to progressive ventricular dysfunction and ultimately heart failure, underscoring the urgent need for regenerative interventions that can replace lost myocardium, attenuate inflammation, and prevent pathological remodeling (Fig. 1) [37–39].

Paracrine effects of MSCs

MSCs exert cardioprotective effects largely through paracrine mechanisms. Secreted factors such as VEGF and HGF stimulate angiogenesis, enhance endothelial survival, and reduce cardiomyocyte apoptosis [29, 40]. Clinical studies also support MSC-induced improvements in perfusion and modest LVEF recovery.

Exosome-mediated anti-fibrotic effects

CSCs and CDCs release exosomes enriched with microRNAs (e.g., miR-146a, miR-21) that regulate inflammatory signaling and suppress fibrosis [41]. Preclinical MI models show that exosome delivery attenuates ventricular remodeling and preserves systolic function.

iPSC-Derived cardiomyocyte replacement

iPSC-derived cardiomyocytes provide a direct source of contractile cells capable of integrating into host myocardium and replacing lost cardiomyocytes after infarction. Preclinical studies have shown that transplanted iPSC-CMs can improve left ventricular contractility, enhance electromechanical coupling, and reduce adverse remodeling by limiting fibrotic scar expansion [42]. In addition, paracrine signaling from iPSC-CMs has been reported to promote angiogenesis and support endogenous cell survival. Recent advances in the metabolic maturation of iPSC-CMs address prior limitations, such as immature electrophysiology [43]. Early-phase studies in Japan demonstrated improved myocardial perfusion and safety during a 3-year follow-up period after transplantation, supporting their translational potential for ischemic cardiomyopathy [44].

Disease mechanisms of AS and stem cell therapeutic targets

AS represents a chronic inflammatory and degenerative vascular disorder in which endothelial injury, lipid accumulation, and immune dysregulation collectively drive plaque development and instability. Stem cell therapy offer multifaceted strategies to counteract these mechanisms by modulating inflammation, repairing endothelium, and stabilizing plaques, thereby providing novel therapeutic opportunities for cardiovascular disease management [45].

Pathophysiology of AS

AS is initiated by endothelial dysfunction, lipid accumulation, and macrophage infiltration, leading to foam cell formation and chronic inflammation. Progressive plaque development eventually destabilizes the vascular wall, predisposing to rupture and thrombosis. Given the multifactorial pathogenesis, stem cell–based interventions aim to address multiple pathological components simultaneously [1].

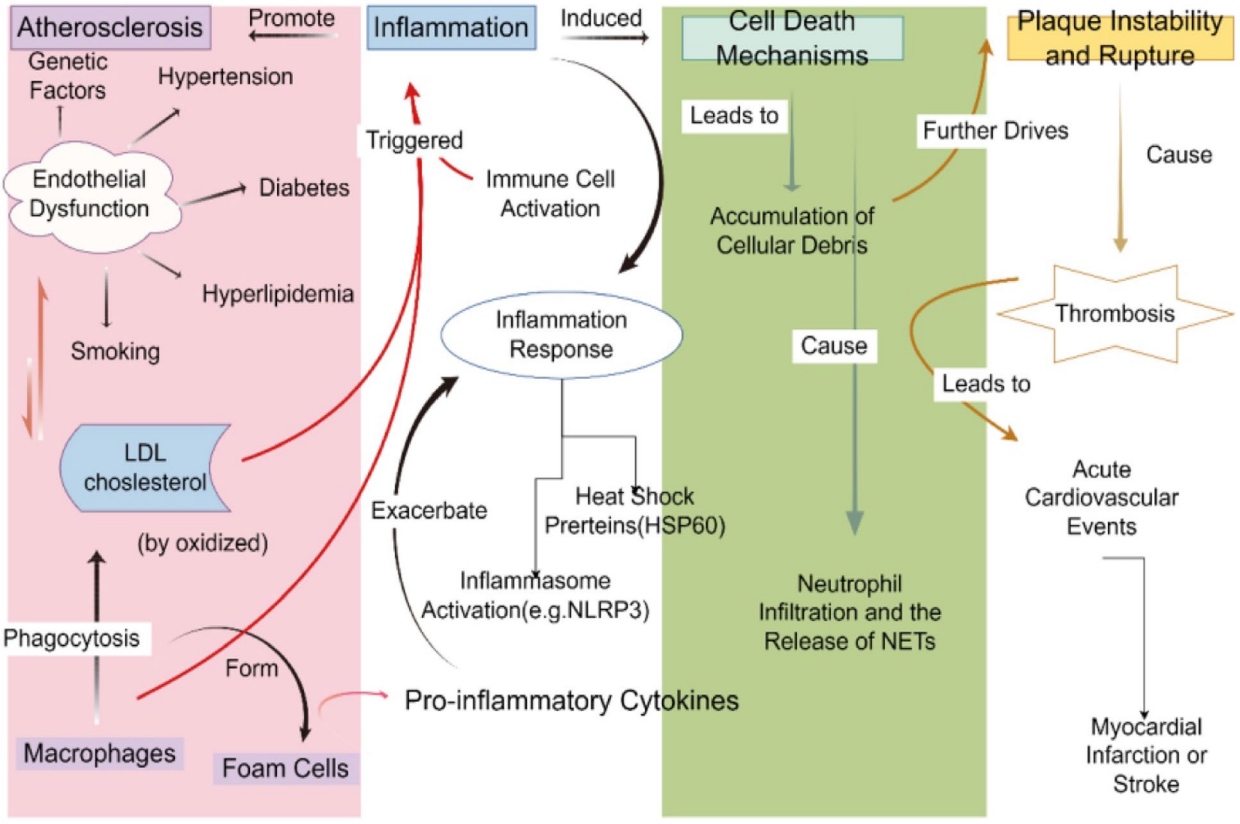

Fig. 1 Interconnected Mechanisms of MI and AS. This figure was drawn by Figdraw. This figure illustrates the interconnected mechanisms of MI and AS, including endothelial dysfunction, inflammation, and regulated cell death, which collectively drive plaque instability and acute cardiovascular events

Immunomodulation by MSCs

MSCs regulate immune homeostasis by promoting macrophage polarization toward the M2 anti-inflammatory phenotype. This shift reduces the release of pro-inflammatory cytokines such as TNF-α and IL-6, thereby attenuating vascular inflammation [46]. Animal studies confirm that MSC treatment reduces plaque burden and improves vascular function through this immunomodulatory pathway.

Endothelial repair via EPCs and iPSC-Derived endothelial cells

Endothelial progenitor cells (EPCs) and iPSC-derived endothelial cells play a pivotal role in vascular repair by accelerating re-endothelialization, promoting neovascularization, and restoring barrier integrity. Clinical trials of EPC infusion in peripheral artery disease and coronary artery disease have demonstrated safety and improved endothelial function [47]. These findings suggest EPC-based therapy could be adapted for atherosclerotic vascular repair.

Plaque stabilization

Beyond reducing plaque volume, stabilizing existing lesions is essential to prevent rupture. Stem cells enhance collagen deposition in fibrous caps and limit necrotic core expansion, thereby improving plaque stability [48]. In preclinical AS models, stem cell therapy has been associated with reduced plaque vulnerability indices, supporting its role in secondary prevention strategies.

Translational outlook

Preclinical models consistently demonstrate that stem cells reduce plaque burden, promote endothelial repair, and stabilize lesions. Early clinical studies confirm safety and feasibility. However, large-scale randomized trials are needed to validate efficacy in patients with advanced AS. Tailoring specific stem cell populations to address immune dysregulation versus endothelial dysfunction might provide the most effective therapeutic approach [45].

Challenges and safety considerations in stem cell therapy

Despite promising advances in preclinical studies and early-phase clinical trials, several critical challenges must be addressed before stem cell therapy can be safely and effectively applied in routine cardiovascular practice. Major concerns include ectopic differentiation and tumorigenesis, immune rejection in allogeneic

transplantation, the lack of standardized quality control in cell manufacturing, and uncertainty regarding long-term safety. Overcoming these barriers through technological innovations, stringent regulatory oversight, and large-scale clinical trials will be essential for the successful clinical translation of stem cell therapy.

Ectopic differentiation and risk of tumorigenesis

After transplantation, iPSCs might differentiate into unintended cell types, such as osteocytes or adipocytes, or even form teratomas [49]. Lineage specificity can be induced by using CRISPR-Cas9 to knock out pluripotency genes such as Octamer-binding transcription factor 4 (Oct4), thereby directing differentiation toward desired cell types. Advances in purification technology have also improved safety. For example, high-throughput sequencing is used to detect gene mutations, while optimized purification protocols reduce the presence of undifferentiated cells [50, 51].

Immune rejection

Allogeneic cell transplantation can trigger immune rejection, necessitating the use of immunosuppressants, which in turn increase the risk of infection. Strategies to reduce immunogenicity include HLA typing and the establishment of high-frequency homozygous iPSC libraries to improve HLA matching between donor cells and recipients. In addition, gene-editing approaches have been employed to generate hypoimmunogenic cell lines, for example, by knocking out HLA loci. Moreover, the inherent immunomodulatory properties of MSCs can be harnessed to mitigate host immune responses [52].

Standardization and quality control

Stem cell therapy involves complex manufacturing procedures and requires the establishment of standardized quality evaluation systems and production processes. The quality evaluation standards for iPSC and their derived cells should be established to ensure the purity and function of the cells. Good Manufacturing Practice (GMP) guidelines dictate that all raw materials and manufacturing procedures must comply with GMP requirements to ensure the safety and consistency of cell products [53, 54].

Long-term safety verification

The long-term safety of stem cell therapy remains a critical consideration for clinical translation. Nevertheless, it is heartening due to the evidence that has been collected to this point. Early clinical trials of MSCs in ischemic cardiomyopathy and heart failure reported no tumorigenic events or severe immune rejection during follow-up periods of up to 5 years [55, 56]. Similarly, transplantation of ESCs-derived cardiac progenitors demonstrated an acceptable safety profile during 1-year follow-up in patients with advanced heart failure [57, 58]. More recently, transplantation of iPSC-derived cardiomyocyte sheets in Japan not only improved myocardial perfusion but also showed no adverse safety signals during 3 years of follow-up [59, 60]. Collectively, these findings suggest that stem cell therapy exhibit a favorable safety profile compared with many conventional interventions, highlighting their translational promise. Nonetheless, large-scale randomized controlled trials with extended follow-up are still required to conclusively evaluate potential late complications such as arrhythmogenicity, ectopic differentiation, and oncogenic transformation. Continued systematic monitoring in clinical cohorts will therefore be essential to establish the long-term safety of regenerative cell therapies.

Discussion

Stem cell therapy exerts disease-specific effects that depend on the underlying pathophysiology. In MI, therapeutic goals include replacing lost cardiomyocytes, attenuating fibrosis, and restoring contractile function. MSCs and CSCs contribute by providing paracrine and exosomal signals that promote angiogenesis and limit adverse remodeling [61]. By contrast, in AS, endothelial dysfunction and chronic inflammation are key drivers of disease progression. EPCs and iPSC-derived endothelial cells play crucial roles in restoring endothelial integrity and stabilizing vulnerable plaques [62, 63]. Despite promising preclinical and early clinical findings, several barriers still hinder translation into routine clinical practice. Cell survival after transplantation is low, with fewer than 10% of MSCs persisting beyond 72 h in ischemic myocardium [64]. In addition, the unresolved risks include ectopic differentiation, arrhythmogenicity, and immune rejection, particularly for pluripotent stem cell–derived products [57]. To overcome these limitations, innovative strategies are being explored. These include biomaterial scaffolds and injectable hydrogels that enhance stem cell retention and survival in hostile ischemic environments, as well as gene-editing approaches such as CRISPR-Cas9, which enable directed differentiation of iPSCs into mature cardiomyocytes and thereby reduce tumorigenic risk [65]. Furthermore, stem cell–derived exosomes enriched with cardioprotective microRNAs have shown efficacy in reducing fibrosis and inflammation, offering a promising cell-free therapeutic alternative [66]. Collectively, these advances highlight both the potential of stem cell therapy to address unmet needs in cardiovascular disease treatment and the importance of continued clinical evaluation and technological refinement to ensure their safe and effective translation into practice [67, 68].

Summary and prospect

In summary, stem cell therapy has shown considerable promise in the treatment of cardiovascular diseases by promoting angiogenesis, modulating immune responses, and facilitating tissue repair [69]. Preclinical and early clinical studies with MSCs, iPSCs, and CSCs have demonstrated encouraging outcomes [70, 71], yet challenges such as limited cell survival, uncontrolled differentiation, immune rejection, and the lack of standardized quality control remain major barriers to widespread clinical translation [27, 72].

Looking ahead, future research will increasingly rely on interdisciplinary innovations. Advances in biomaterials and 3D bioprinting may improve cell survival and integration [19], while gene-editing technologies such as CRISPR-Cas9 enable precise lineage commitment and reduce tumorigenic risk. Exosome-based, cell-free therapies enriched with cardioprotective microRNAs represent a particularly promising alternative to direct cell transplantation [73, 74]. Similarly, although outside the cardiovascular domain, findings from independent investigators indicate that intravenous infusion of autologous menstrual blood–derived stem cells (MenSCs) can effectively ameliorate menopausal symptoms through multi-pathway immune–endocrine modulation, highlighting a novel clinical application of stem-cell therapy in menopausal syndrome [75]. Moreover, the integration of single-cell omics, artificial intelligence, and precision medicine is expected to accelerate personalized approaches and refine patient selection. Collectively, these advances highlight a future in which stem cell–based and cell-free regenerative therapies become safe, effective, and routine options in cardiovascular disease management [76, 77].

Acknowledgements
The authors declare that they have not use AI-generated work in this manuscript.

Author contributions
Xingchen Wan, Chenyan Qian, and Siyi Liu: Framework construction, literature collection, collation of data, draft-writing. Yue Xu, Jinghua Yuan: Review & editing. Xinling Zhang, Xiaoping Li: resources, writing-review and editing, supervision, project administration, and funding.

Funding
This study was financially supported by Zhejiang Shuren University Basic Scientific Research Special Funds (2024XZ011). The funder did not participate in the designing, performing or reporting in the current study.

Declarations

Conflict of interest
The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 25 April 2025 / Accepted: 12 September 2025
Published online: 09 October 2025

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