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Innovative approaches to boost mesenchymal stem cells efficacy in myocardial infarction therapy

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A B S T R A C T

Stem cell-based therapy has emerged as a promising approach for heart repair, potentially regenerating damaged heart tissue and improving outcomes for patients with heart disease. However, the efficacy of stem cell-based therapies remains limited by several challenges, including poor cell survival, low retention rates, poor integration, and limited functional outcomes. This article reviews current enhancement strategies to optimize mesenchymal stem cell therapy for cardiac repair. Key approaches include optimizing cell delivery methods, enhancing cell engraftment, promoting cell functions through genetic and molecular modifications, enhancing the paracrine effects of stem cells, and leveraging biomaterials and tissue engineering techniques. By focusing on these enhancement techniques, the paper highlights innovative approaches that can potentially transform stem cell therapy into a more viable and effective treatment option for cardiac repair. The ongoing research and technological advancements continue to push the boundaries, hoping to make stem cell therapy a mainstream treatment for heart disease.

1. Introduction

Heart failure has become a worldwide health crisis, responsible for 31 % of global deaths [1]. Myocardial infarction (MI), the most prevalent form of acute heart injury, is a leading cause of heart failure [2]. MI caused by various injuries triggers a complex wound-healing process to restore homeostasis [3]. While collagen deposition is a normal and essential component of the wound-healing process, it can develop into an increasingly irreversible fibrotic response over time. Excessive accumulation of collagen after cardiac injury causes cardiac dysfunction, leading to increased rates of arrhythmias and sudden cardiac death, becoming a major factor in the progression of heart failure [4,5]. Although medications and interventional therapies can alleviate symptoms and complications, such as arrhythmias, to prevent sudden cardiac death, these approaches mainly postpone mortality [6]. They do not fundamentally address the ongoing loss of myocardial cells or the progressive deterioration of cardiac function following MI [7]. While heart transplantation is the most direct and effective method, it is limited by donor availability and post-transplant immune rejection issues [8]. Human cardiomyocytes (CMs) can regenerate throughout life, starting with an annual turnover rate of approximately 1 %, which gradually declines to 0.3 % by age 75 [9]. MI results in the loss of 20 %–40 % of myocardial cells within a few hours, making it impossible for the damaged myocardial tissue to self-heal through cellular proliferation, ultimately leading to heart failure [10]. Given the limited regenerative ability of mature cardiomyocytes, stem cell therapy offers an innovative treatment strategy for many patients with cardiac injury by delaying myocardial apoptosis or inducing the regeneration of myocardial cells to repair the damaged myocardium [11,12].

Stem cell therapy for cardiac injury has evolved from basic research and animal studies to human clinical trials with promising, albeit varied, results (Table 1). In 2004, the Texas Heart Institute received the first

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Food and Drug Administration (FDA) approved clinical trial of autologous adult stem cell therapy for congestive heart failure in the United States [13]. In 2011, the South Korean Ministry of Food and Drug Safety approved Cellgram-AMI, a stem cell-based therapeutic drug developed by Pharmicell Co., Ltd. This was a groundbreaking moment as Cellgram-AMI became the first stem cell drug in the world to receive approval for treating acute myocardial infarction (AMI) [14]. In 2015, the Japanese company Terumo Corporation developed Heart Sheet, the world's first regenerative medical product for treating heart failure, which was approved for production and sale [15]. In 2023, the Texas Heart Institute revealed the findings of the largest cell therapy trial for heart failure, demonstrating that stem cells can enhance long-term outcomes for heart failure patients while significantly decreasing the risk of heart attacks and strokes [16]. However, many challenges remain in stem cell therapy for MI. For example, in studies on humans and large animals, the retention and survival of transplanted cells in the heart are poor, with only 10 % retention and survival after 1 h of injection [17–19]. Even if cells are retained in the damaged myocardial tissue, they may face a relatively harsh tissue microenvironment [20]. Moreover, the potential mechanisms of stem cell therapy for MI remain to be further explored; addressing these issues will help accelerate the clinical application of this therapy.

Stem cell therapy for MI has evolved from basic research and animal studies to human clinical trials with promising, albeit varied, results. Researchers are employing various strategies to enhance the efficiency of stem cell therapy for MI, focusing on optimizing cell types and delivery methods, improving cell survival and integration, reducing immune responses, leveraging combination therapies, personalizing treatments, and refining regulatory and manufacturing processes. These efforts are focused on addressing current challenges and enhancing the effectiveness of stem cell-based therapies for heart disease. This article reviews the advancements and ongoing challenges in stem cell therapy for myocardial infarction. It explores how researchers are refining various strategies to enhance the effectiveness of stem cell treatments.

2. The pathological changes and progression of MI

Cardiomyocytes (CMs) depend on oxidative metabolism for energy production and are particularly sensitive to fluctuations in oxygen levels [25]. When coronary artery occlusion reduces blood supply and decreases myocardial oxygen levels, cells increase anaerobic metabolism to maintain energy levels, often leading to harmful consequences, including the loss of myocardial cell function and the release of intracellular contents into surrounding tissues (Fig. 1) [8]. This, in turn, triggers an acute immune response, causing structural and functional alterations in the heart to maintain cardiac prognosis [26]. Because of the heart's limited regenerative ability, the infarcted area experiences significant remodeling, characterized by hypertrophy of the surrounding myocardium and the development of dense fibrotic scars. These changes serve as compensatory mechanisms in response to pathophysiological alterations. This process, called cardiac remodeling, is a complex phenomenon in which the heart's structure, shape, and function undergo significant changes [27]. In the early stages, changes in cardiac function can be detected within hours to days. Myocardial necrosis induces a massive accumulation of inflammatory cells, leading to the destruction of the collagen scaffold, alterations in ventricular shape, localized thinning, and expansion of the myocardial infarction area [28,29]. Over the next few weeks to months, there is heightened activation of proteases and an increase in cytokine expression. During the later stages, reactive myocyte hypertrophy, interstitial fibrosis, and left ventricular dilation occur [30]. Therefore, the pathological process of myocardial infarction will be discussed in stages: including the inflammatory, proliferative (sometimes referred to as anti-inflammatory), and remodeling (sometimes referred to as maturation) phases [28,29,31](Fig. 1).

2.1. Inflammatory phase

Acute myocardial ischemia and hypoxia caused by thrombosis or vascular occlusion led to sudden cell necrosis in the infarcted area. Necrotic myocardial cells release inflammatory factors that trigger an inflammatory response (Fig. 1, Stage 1). Resident cardiac macrophages start to die from ischemia within 24 h after the infarction. Meanwhile, monocytes from the bloodstream are recruited to the infarcted area, where they differentiate into macrophages [26]. These macrophages clear cell debris (phagocytosis) and secrete cytokines such as TNF-α, IL-1β, and IL-6 that amplify the inflammatory response. However, they also release signals that trigger the inflammation resolution and initiate tissue repair. For example, M1 cells are polarized to the M2 type, which can secrete IL-10 and growth factor TNF-β (Fig. 1, Stage 2). In addition, Neutrophils also arrive first and release enzymes and reactive oxygen species (ROS) to clear dead cells and debris, but they can also exacerbate tissue damage [28]. While inflammation is essential for clearing dead tissue and initiating repair, excessive or prolonged inflammation can lead to further damage and adverse remodeling of the heart tissue [32]. Understanding the inflammatory phase has led to the development of therapies to modulate inflammation to improve outcomes after MI. It has been shown that shortening the inflammatory phase and accelerating the onset of the anti-inflammatory phase are vital for improving the long-term prognosis in both patients and animal models of MI [29].

2.2. Proliferative phase

The proliferative phase, also known as the anti-inflammatory phase, occurs from days 1–3 post-myocardial infarction. During this phase, the body shifts from an inflammatory response to an anti-inflammatory, essential for restoring the integrity of the injured heart tissue [33]. During this period, the release of pro-inflammatory factors decreases, creating a more favorable environment for healing. Anti-inflammatory

Table 1
Stem cell therapy in the treatment of cardiac injury.

Timeline	Disease	Types of stem cell	Delivery strategies	Efficacy	Ref.
2004	Congestive heart failure	Autologous adult bone marrow stem cells, BM-MSCs	Transendocardial injection	Improvement in cardiac function in patients undergoing off-pump coronary artery bypass grafting	[13, 21]
2011	AMI	Autologous BM-MSCs	Reperfused by coronary angioplasty	Improvement of Left Ventricular Ejection Fraction, LVEF	[14]
2014	Chronic ischemic cardiomyopathy	Adipose mesenchymal stem cells, AD_MSCs	Transendocardial injection	Increase in LV total mass No significant change in LVEF	[22]
2015	Serious heart failure	Autologous skeletal myoblast	Using cell sheet technology	Improvement in LVEF	[15]
2017	Heart failure	Umbilical cord mesenchymal stem cells, UC-MSCs	Intravenous Infusion	Improvements in LVEF No changes in LV volumes	[23]
2019	Refractory angina	AD_MSCs	Intra-myocardial injection	Improvement in cardiac symptoms and unchanged exercise capacity	[24]
2023	Heart failure with reduced ejection fraction	Mesenchymal precursor cells	Transendocardial delivery	Reduced major adverse cardiovascular event and systemic inflammation in patients with heart failure	[16]

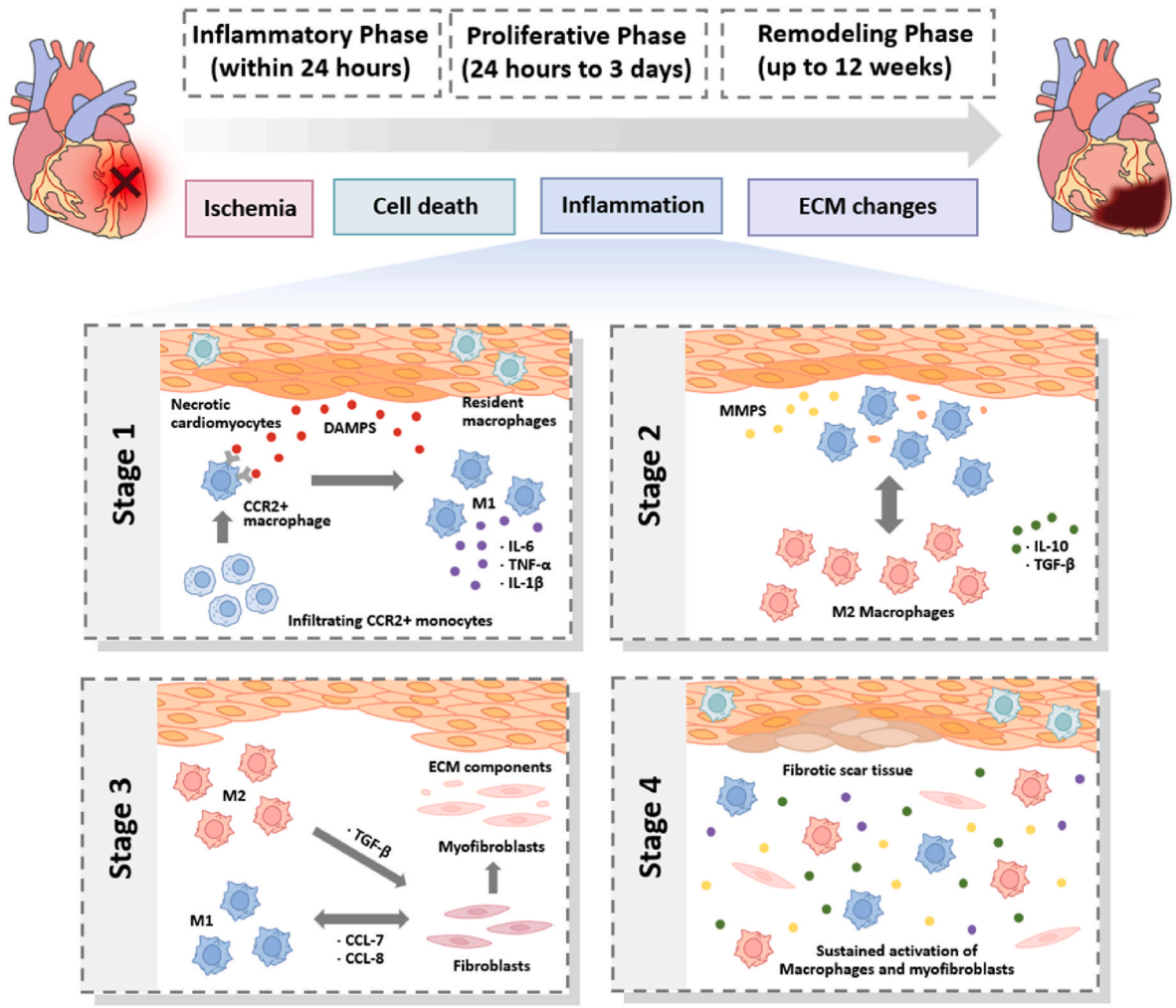

Fig. 1. The pathological changes and progression of MI. These changes include the inflammatory (within 24 h), proliferative (24 h–3 days), and remodeling phases (up to 12 weeks). Myocardial infarction (MI), commonly referred to as a heart attack, occurs when blood flow to a section of the heart muscle is obstructed, leading to oxygen deprivation, cell injury, and tissue damage. This damage then triggers inflammatory signaling pathways that initiate an immune response. Stage 1, cell necrosis and release of damage-associated molecular patterns (DAMPs) to recruit $CCR2^{+}$ monocytes. Monocytes differentiate into pro-inflammatory macrophages type-1 (M1) and secrete interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interleukin-1β (IL-1β) (pro-inflammatory cytokines); Stage 2, macrophages type-1 (M1) perform phagocytosis to clear necrotic cell debris and secrete matrix metalloproteinases (MMPs) to induce extracellular matrix (ECM) breakdown. One part of the M1 cells are polarized to the macrophage type-2 (M2), which can secrete interleukin-10 (IL-10) (anti-inflammatory cytokine) and Tumor Necrosis Factor-beta (TNF-β) (growth factor). Stage 3, the M1 cells release chemokines to recruit activated fibroblasts, while M2 cells enhance the activation of myofibroblasts. These myofibroblasts may contribute to the secretion of ECM components, aiding in tissue repair. Stage 4, After the removal of cellular debris and resolution of the inflammatory response, myofibroblasts, along with macrophages and other cell types, collaborate to form and break down scar tissue that will replace the damaged region. Adapted from O'Rourke et al. [26] and created by Microsoft PowerPoint.

factors (such as IL-10) increase to promote the resolution of inflammation and the initiation of tissue repair (Fig. 1, Stage 2) [34]. Under pathological conditions, cardiac fibroblasts (CFBs) differentiate into myofibroblasts (MFBs), which increases the expression of contractile proteins like α-smooth muscle actin (αSMA), and boosts the deposition of extracellular matrix (ECM) proteins, such as type I collagen and fibronectin, ultimately leading to scar tissue formation [31,35]. In all stages of MI, Macrophages are the primary immune cell type [36]. For example, macrophages secrete tissue inhibitors of metalloproteinases (TIMPs), which prevent collagen degradation by inhibiting the proteolytic activity of MMPs [37]. Macrophages also stimulate ROS production, activate NF-κB, and lead to more inflammatory cell accumulation [38,39]. Therefore, the prompt transition of M1 macrophages to anti-inflammatory M2 macrophages is essential for clearing dead cells, promoting anti-inflammatory responses, and facilitating tissue repair. In the proliferative stage, the suppression and resolution of inflammation are accompanied by the migration of numerous resident CFBs to the damaged area, where they differentiate into MFBs and start synthesizing large quantities of ECM for tissue repair (Fig. 1, Stage 3) [29]. Therefore, both the inflammatory and proliferative phases during the early stages of MI profoundly influence the degree of tissue remodeling, wound healing, and cardiac functional preservation in human and mouse models of MI.

2.3. *Remodeling phase*

Weeks later, the remodeling phase is the final healing stage following MI. During this phase, cell debris is cleared from the infarcted area, and the inflammatory process is suppressed; collagen fibers form in the infarcted region, replacing necrotic cells (Fig. 1, Stage 4) [40]. With the secretion of various TIMPs and MMPs to alter the ECM, the infarcted area undergoes extensive remodeling, which can significantly impact the heart's function and is a major determinant of long-term patient outcomes [41]. Following the loss of cardiomyocytes (CMs), rapid

fibrosis is needed to prevent ventricular expansion and rupture [27]. The progress of fibrotic scar formation depends on the balance of remodeling processes, and unbalanced ECM generation and degradation can impair cardiac function [42]. The population of monocytes and macrophages recruited to the infarct site typically returns to baseline levels within 14 days, although they may remain in the myocardium for months following MI [43,44]. Excessive inflammation during the first two weeks after a myocardial infarction often results in irreversible cell damage and harmful tissue remodeling, which can lead to the development of additional cardiac issues within a few years. Researchers suggest that minimizing inflammation-induced damage in the initial days after myocardial infarction—by controlling the early inflammatory cascade triggered by macrophage activity—can help reduce long-term cardiac dysfunction in the following years [29].

3. Stem Cell therapy for myocardial infarction (MI)

After an MI, the human heart's endogenous regenerative capacity is insufficient to replace the abnormal tissue, resulting in fibrotic and non-contractile scars [17]. Stem cell-based therapies offer significant potential in enhancing endogenous repair and regenerating damaged tissue, making them a promising approach to reducing the incidence and mortality associated with cardiovascular diseases [10,45]. Stem cells possess three key characteristics: originating from a single cell, self-renewing, and the ability to differentiate into specialized cell types. In response to injury or specific physiological conditions, stem cells play a vital role in the body's repair system by activating or replenishing other cells as required [46]. The initial hypothesis in stem cell research for MI was that stem cells could differentiate or transdifferentiate into mature cells, such as cardiomyocytes and endothelial cells, and then integrate into the damaged heart tissue to restore normal heart function. While this concept spurred much of the initial research, later findings suggested that the primary benefits of stem cells might derive from the paracrine effects—where the stem cells release signaling molecules that promote healing, reduce inflammation, and recruit the body's repair mechanisms—rather than from direct differentiation and integration (Fig. 2) [47,48]. While these findings provide insights into how stem cell therapy might benefit patients with MI, ongoing research is necessary to fully comprehend the underlying mechanisms, refine treatment strategies, and ensure both safety and efficacy.

3.1. Types of stem cells

Currently, the primary types of cells used in treating MI include mesenchymal (MSCs), embryonic (ESCs), and induced pluripotent (iPSCs) stem cells [49]. ESCs and iPSCs are pluripotent stem cells with a high differentiation potential. However, human ESCs face numerous challenges in clinical applications primarily due to legal and ethical concerns, along with their restricted availability [50]. iPSCs are generated by reprogramming mature cells through genetic modification. Theoretically, they offer a potential source for various cell types due to their multiple differentiation capabilities [51]. However, iPSCs possess a high proliferation capacity and pluripotency, which can pose a risk of tumorigenesis in vivo due to their genetic instability [52,53]. To address this issue, iPSCs should ideally undergo differentiation before being delivered to the target tissues [50]. MSCs can be obtained from various sources, including umbilical cord (Umbilical cord mesenchymal stem cells, UC-MSCs), bone marrow (Bone marrow mesenchymal stem cells, BM-MSCs), adipose tissue (Adipose mesenchymal stem cells, AD-MSCs), hair follicles (Hair follicle mesenchymal stem cells, HF-MSCs), and dental pulp (Dental pulp mesenchymal stem cells, DP-MSCs) [54]. MSCs possess regenerative capabilities and offer numerous benefits, including

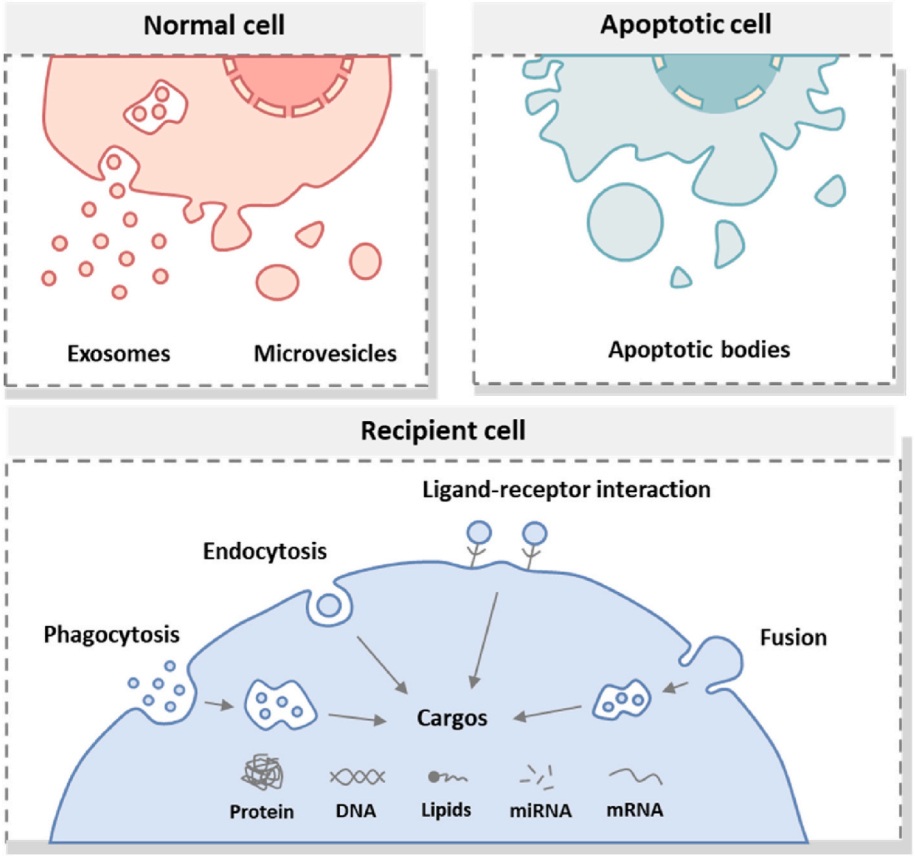

Fig. 2. The extracellular vesicles (EVs) released from cells to achieve intercellular communication. EVs, including exosomes and microvesicles, can be absorbed by target cells through endocytosis, membrane fusion, or phagocytosis. Created by Microsoft PowerPoint.

low immunogenicity, immunomodulatory properties, and the ability to influence neighboring cells through paracrine signaling [55].

3.2. MSCs secretome

MSCs can be identified by surface markers (such as CD44, CD73, CD90, and CD105) and potential differentiation (osteogenic, chondrogenic, and adipogenic differentiation) [56]. It is now generally acknowledged that MSCs primarily exert their therapeutic effects through paracrine mechanisms [57,58]. MSCs secrete soluble factors, including cytokines, chemokines, growth factors, and vesicular secretions known as EVs, which can be isolated from the collected cell culture medium [59,60]. This MSC-conditioned medium has demonstrated that it can enhance cell proliferation and migration while exhibiting anti-apoptotic and anti-inflammatory effects in vitro (Fig. 3) [61]. Anti-apoptotic factors include vascular endothelial growth factor (VEGF), stromal cell-derived factor-1α (SDF-1α), monocyte chemoattractant protein (MCP-1), interleukin-6 (IL-6), and hepatocyte growth factor (HGF); factors promoting proliferation and migration include SDF-1α, MCP-1, IL-6, interleukin-8 (IL-8), angiopoietin-1 (AGPT-1), macrophage inflammatory protein (MIP-1α), HGF, placental growth factor (PIGF), insulin-like growth factor (IGF-1), tumor necrosis factor-stimulated gene/protein 6 (TSG-6), VEGF, sphingosine-1-phosphate (S1P), basic fibroblast growth factor (FGF2), and platelet-derived growth factor (PDGF); pro-angiogenic factors include VEGF, FGF2, SDF-1α, transforming growth factor-β (TGF-β1), IGF, MCP-1, AGPT-1, HGF, IL-6, and IL-8; anti-inflammatory factors include TGF-β1, prostaglandin E2 (PGE2), indoleamine 2,3-dioxygenase (IDO), and TSG-6 [59]. Additionally, EVs are nanoscale particles secreted by cells, typically containing lipids, proteins, and nucleic acids, and are considered to have functional activity as intercellular messengers (Fig. 2) [58,62]. Currently, exosomes, which range in size from 50 to 150 nm, are generated when multivesicular bodies fuse with the plasma membrane. In contrast, microvesicles, measuring 100–1000 nm, are released directly from the outward budding of the plasma membrane [63]. Apoptotic bodies, which can reach up to 2 μm in diameter, arise from the blebbing of the plasma membrane in apoptotic cells, with their contents varying depending on the cell type [64].

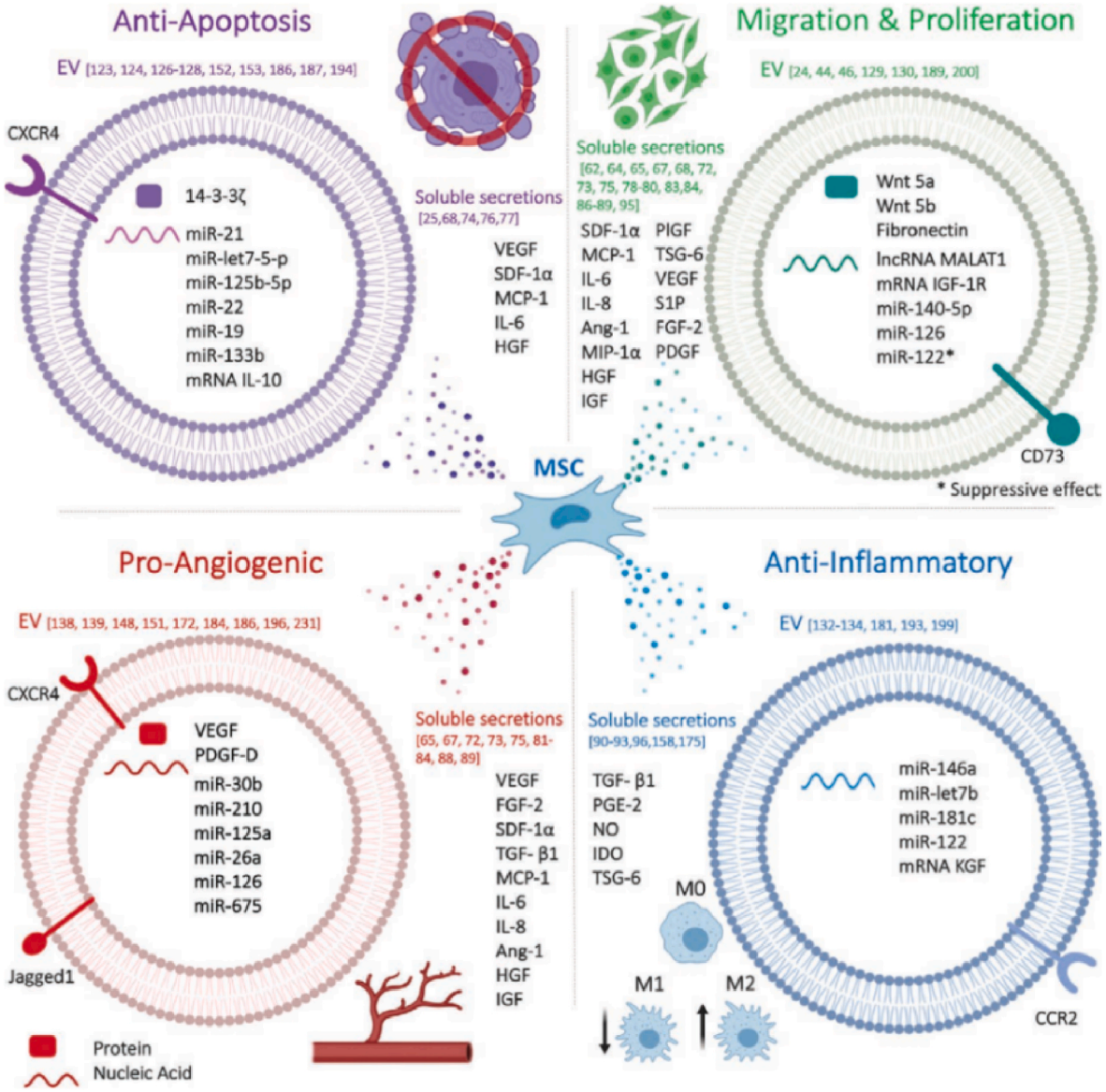

Fig. 3. MSC-secreted soluble factors and functional extravascular vesicles (EVs) mediate tissue repair, including anti-apoptosis, cell proliferation and migration, pro-angiogenesis, and anti-inflammatory effects [61]. Copyright 2020, Wiley.

3.3. Stem Cell delivery strategies

Currently, stem cells can be introduced into the body using various methods. Among these approaches to improve the efficacy of cell therapy, the main objective is to retain the cells at the targeted location [18]. However, due to low cell homing rates, most cells are either quickly flushed out by the heart, transferred from the injection site through lymphatic or vascular pathways, or die at the targeted site, resulting in low cell retention rates (Fig. 2) [65]. In other words, factors leading to cell loss include "washout" effects, low cell injection efficiency, and cell death due to hash local microenvironment. In animal and clinical trials, less than 10 % of cells can reserve in the heart 24 h after treatment [66,67]. Additionally, the body's immune response may identify and eliminate transplanted cells. Immune cells at the site of myocardial injury, such as macrophages and neutrophils, can secrete cytotoxic factors that induce apoptosis in transplanted cells [68,69]. Besides inflammatory cells, the infarcted area with reduced pH, increased levels of matrix metalloproteinases, and an excess of ROS can lead to apoptosis of transplanted cells [20]. The infarcted region's lack of extracellular matrix microenvironment, poor blood supply, and hypoxia also contribute to the inability to support cell survival [70]. The priority of delivery strategies must ensure that cells are successfully delivered to the target site and exert therapeutic effect (Table 1).

3.3.1. Intravenous Cell delivery

Intravenous cell injection is the most used method in cell therapy. It is a systemic delivery route that is minimally invasive, allowing for prompt and on-demand administration [71]. After intravenous injection into the circulatory system, stem cells are transported to the ischemic infarcted area, where homing occurs [72]. However, stem cells transported through the circulatory system may accumulate in various body parts, particularly in the lungs, because of the Pulmonary First-Pass Effect [66], with only a small fraction of cells reaching the infarcted heart. Despite the low retention rate of stem cells in situ, Luger et al. investigated the impact of intravenously injected MSCs on left ventricular function (LVF) following MI, indicating that intravenous MSC administration could reduce the progressive decline in LVF and adverse remodeling after acute MI in mice, as well as enhance LVF in ischemic cardiomyopathy, partly due to systemic anti-inflammatory effects [73]. Xie et al. identified a marker distinguishing a subpopulation of BMSCs known for their strong migratory capabilities. The results indicated that MSCs marked with CD51 ($CD51^+$ MSCs) had better proliferation ability than $CD51^-$ MSCs. $CD51^+$ MSCs preferentially migrated to the infarcted heart 48 h after intravenous injection and stayed in the infarcted heart for as long as eight days, improving left ventricular ejection fraction (LVEF) and left ventricular fractional shortening (LVFS) [74]. It was suggested that both the type of transplanted cells and the homing mechanism are essential for intravenous injection. Although intravenous delivery often leads to cell accumulation in other organs, resulting in low efficiency in reaching the heart [65], this method's non-invasive nature allows for repeated cell administration. However, further research is necessary to establish the optimal timing for therapeutic effectiveness.

3.3.2. Intracoronary injection

Intracoronary injection, a widely used method for cell delivery, involves administering cells through a coronary catheter positioned near the ischemic area [65]. Due to its minimally invasive nature, this method is widely accepted in clinical practice and can deliver more cells to the injured site. However, after delivery, transplanted cells must pass through capillaries to reach the infarcted area, but blood capillaries often cause blockages, preventing other cells from entering the tissue [49]. Moreover, the high arterial pressure may easily flush the cells out of the heart. Additionally, stem cells first need to go home to the vascular wall and then be transported to the infarcted area. Campbell et al. quantitatively assessed the retention of donor cells of different sizes following intra-coronary injection using a perfused rat heart system [75]. The results showed that 5 min after injection, the retention rate for bone marrow mononuclear cells (a median diameter of 7.0 μm) was 20.1 %, while the retention rate for BMSCs (a median diameter of 11.5 μm) was three times higher, reaching 77.5 %. This may be because cells can get lodged within the blood vessels (with coronary capillary diameters ranging from 5 to 10 μm, and even smaller in rodents), thus improving cell retention rates.

3.3.3. Intramyocardial injection

Cells can be delivered into the infarcted heart either through the epicardial side or via a needle catheter from the endocardial side (Fig. 4). This approach is one of the most straightforward ways to deliver cells to the heart sites and has been extensively utilized in animal studies and clinical trials [76]. This method overcomes the limitations of coronary cell injection (cell washout, low homing rate), improving cell retention. However, cells delivered in suspension may be unevenly distributed in the infarcted area, potentially impacting myocardial structure and function. Additionally, intramyocardial injections using needles or catheters might result in extra damage to heart tissue, leaving puncture marks from which cells may be expelled by the heart's cyclical contractions. What's worse, myocardial injection carries risks such as ventricular perforation.

Moreover, researchers are also working on developing innovative cell delivery approaches: cell sheet transplantation and intrapericardial injection. Compared to intramyocardial, intracoronary, and intravenous injections, cell sheet transplantation has been shown in many animal studies to offer minimally invasive cardiac transplantation with higher cell retention rates [77–79]. Similarly, intrapericardial injection leverages the microenvironment of the pericardium, which is conducive to cell growth and migration, to improve the efficacy of stem cell therapy for MI [80]. The pericardium encases the heart, shielding it from the intrathoracic environment. The area between the pericardial parietal layer and the heart is the pericardial cavity, filled with pericardial fluid that minimizes friction between the heart and surrounding tissues [81]. The components of pericardial fluid are favorable for cell survival and function [82]. In contrast to intramyocardial injection, the greater volume of the pericardial cavity can accommodate more cells, making it less likely for cells to be expelled. Zhu et al. investigated the therapeutic effect of intrapericardial injection of iPSCs-derived cardiac progenitor cells in an MI rodent model [80]. After injection, they integrated this method with hydrogel injection, which creates a heart patch-like structure in the pericardial cavity, thereby reducing immune response, enhancing the retention of therapeutic agents in the heart, and improving cardiac remodeling and function following MI. Li et al. explored the feasibility and safety of intrapericardial injection using a minimally invasive procedure in an animal model, enhancing the clinical translatability of the intrapericardial delivery route. The result showed that MSCs delivered via the intrapericardial route achieved a tenfold higher engraftment rate (42.5 $\pm$ 7.4 %) compared to MSCs injected intramyocardially (4.4 $\pm$ 1.3 %) [83].

Cell sheet transplantation and intrapericardial injection technology also face challenges that impact their effectiveness and broader application. Maintaining tissue slices' structural integrity, viability, and physiological relevance in cell sheet transplantation is challenging due to the lack of vascularization, leading to limited replication of in vivo conditions [84,85]. Additionally, variability in slice preparation and donor differences can affect reproducibility and scalability for clinical applications [86]. Intropericardial injection technology, while promising for targeted delivery, encounters risks such as cardiac tamponade, uneven distribution, and potential pericardial reactions like inflammation or fibrosis [87,88]. The invasive nature of the procedure also poses safety concerns and limits its suitability for certain patients, while technical precision and regulatory hurdles further complicate its adoption. Hence, both technologies require advancements in methodology, safety, and standardization to overcome these barriers and achieve their

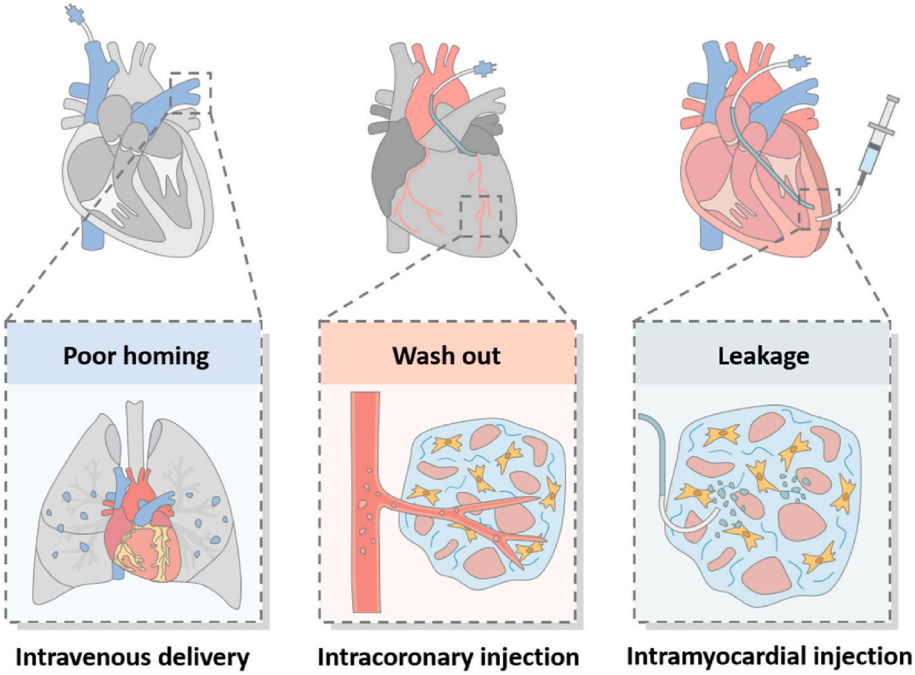

Fig. 4. Different Stem Cell Delivery Strategies. The reasons for the low cell retention rate at the site of heart injury are poor homing, washout, and leakage. Left, intravenous delivery; Center, intracoronary injection; Right, Intramyocardial injection. Adapted from Li et al. [65] and created by Microsoft PowerPoint.

full potential.

Each stem cell delivery strategy has unique advantages and disadvantages, making them appropriate for various clinical scenarios (Table 1). The choice of the proper delivery route depends on factors such as heart disease type, the desired therapeutic outcome, and the patient's overall health condition. Ongoing research must refine these delivery methods to maximize their therapeutic potential while minimizing associated risks.

4. Strategies to enhance the therapeutic potential of stem cells

Although previous studies have shown that stem cells, particularly MSCs, offer significant benefits for treating MI, their efficacy has not yet reached satisfactory levels. This may be due to the injection method, where most cells cannot effectively migrate or remain at the infarct site. Additionally, the myocardium undergoes complex pathological changes after infarction, exhibiting pathological features such as ischemia and inflammation during the acute phase of MI. Ischemia-induced oxidative stress and damaging cytokines can result in the death of implanted cells, prompting the exploration of various strategies to improve the therapeutic efficacy of stem cells (Fig. 5) [89]. These include physical/chemical methods, growth factors, drugs, and genetic engineering strategies to prime stem cells, which increase cell survival and function after transplantation [70]. Moreover, advanced functional biomaterials can transport stem cells to target tissues/organs, promoting their survival, differentiation, and integration with host tissues, which may improve the clinical outcomes of stem cell therapies.

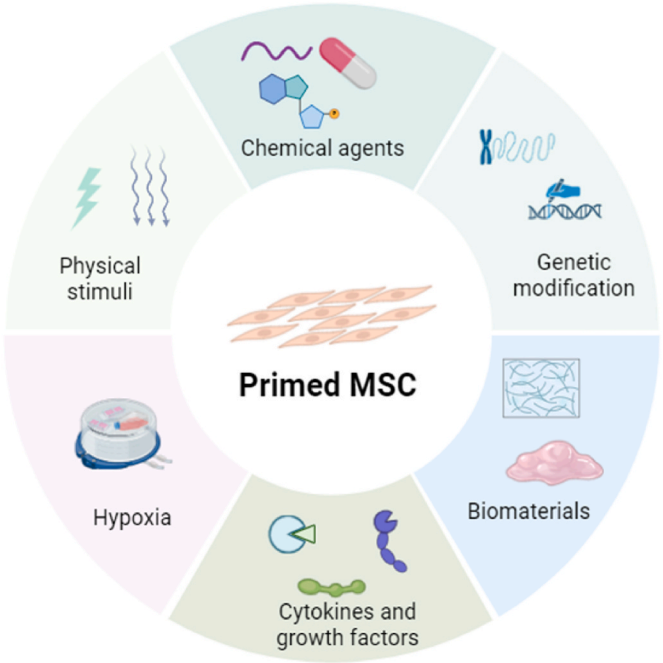

Fig. 5. Schematic illustration of available strategies to promote the therapeutic efficacy of MSCs, Created by biorender.

4.1. Physical processing methods

Stem cells can be preconditioned through physical methods, including light, magnetic fields, heat, and oxygen concentration control. Low-level laser therapy (LLLT) and red or near-infrared lasers within the wavelength range of 600–1100 nm can be applied to cells, yielding beneficial effects such as cell proliferation, improved adhesion, and the prevention of apoptosis [90]. Exposure of MSCs to pulsed electromagnetic fields (PEMF) may allow the magnetic field to propagate and effectively amplify along the entire signal pathway, altering cell behavior [91]. Research has shown that PEMF can modulate the expression and activation of cell surface receptors and their associated signaling pathways, ultimately restoring homeostatic cell functions. Short-term exposure of cells to mild heat stress (42°C–43 °C) can induce upregulation of heat shock protein (HSP) genes, improving the survival rate of transplanted MSCs [92]. Additionally, oxygen is essential for cell survival. Hypoxia treatment decreases the viability and proliferation of MSCs, but subsequent reoxygenation can improve cell survival. This ongoing cycle of hypoxia and reoxygenation can yield several beneficial

effects on MSCs, such as enhanced survival and proliferation, increased secretion of angiogenic factors, and improved homing ability, enabling MSCs to endure challenging microenvironments in vivo [93]. Hu et al. found that transplantation of hypoxia-preconditioned MSCs significantly improved cardiac function and remodeling in non-human primates, boosted cardiomyocyte (CM) functions, enhanced angiogenesis and CM metabolism, and reduced inflammation without increasing the incidence of arrhythmias [70]. Hu et al. were the first to show in humans that intracoronary administration of hypoxia-preconditioned autologous BMSCs significantly delayed left ventricular remodeling in acute MI patients without increasing the incidence of major adverse cardiovascular events [94].

Besides the physical factors mentioned above, mechanical signals enhance stem cells' therapeutic potential [95]. The hydrostatic pressure, microgravity, tension, shear stress, and stiffness of the substrate or extracellular matrix (ECM) profoundly influence stem cell fate through mechanosensing mechanisms [96]. For example, stem cells sense and respond to substrate stiffness via focal adhesions and cytoskeletal tension, activating mechanotransduction pathways such as YAP/TAZ and RhoA/ROCK signaling [97]. Tunable hydrogels and dynamic stiffness systems have been developed to provide precise control over mechanical cues [98,99]. Exposing stem cells to specific mechanical forces before implantation primes them for improved functionality and integration in vivo [100]. Cyclic stretching encourages differentiation into vascular smooth muscle and cardiac cells [101]. Shear stress enhances endothelial differentiation and angiogenesis [102].

4.2. Chemicals processing methods

Chemical/pharmacological molecules are easy to use and can effectively enter cells. Non-immunogenic, cost-effective, and efficient drugs are commonly used methods for stem cell preconditioning (Table 2). For example, certain drugs can protect cells from oxidative stress-induced damage, including trimetazidine, diazoxide, vitamin E, and carvedilol. Trimetazidine enhances pro-survival factors like HIF-1α, Akt, and Bcl-2 [103–107]. Diazoxide can open/activate mitochondrial ATP-sensitive potassium channels [106]. Vitamin E and carvedilol have antioxidant properties [108–110]. Chemical hypoxia-inducing agents provide an alternative to hypoxia incubators or chambers for stem cell preconditioning. Several chemical hypoxia-inducing agents, including 4-dinitrophenol (DNP) [111–113], deferoxamine (DFO) [114–116], dimethyloxalylglycine (DMOG) [117–119], isoflurane (ISO) [120], and cobalt chloride ($CoCl_2$) [121–123], can be used to induce tissue hypoxia. These hypoxia agents can increase cell proliferation, or enhance differentiation, increase migration, and induce angiogenesis after treating stem cells [124]. This preconditioning can effectively mitigate the side effects of drug administration in vivo, regulate drug dosage, and enhance therapeutic efficacy. Selecting drugs, specific preconditioning conditions, and underlying mechanisms require further research. Compounds can also directly reprogram one cell type into another by modulating cellular signaling pathways and epigenetic modifications without needing transgenes [125–129]. Statins are well-known lipid-lowering drugs that have shown beneficial effects on MSC behaviors such as apoptosis, proliferation, migration, and differentiation (Table 3) [130]. In MI treatment studies, statin-MSC combined therapy improved cardiac function and repair [131,132] (see Table 4). The specific mechanisms and signaling pathways through which statins affect MSCs differ. Gaining a deeper understanding of these pathways and mechanisms will facilitate the use of statins in tissue engineering and cell therapy.

Table 2
Advantages and disadvantages of stem Cell delivery strategies.

Strategies	Advantages	Disadvantages
Intravenous delivery	Non-invasive	Low targeting efficiency Limited retention
	Repeatability	Unintended effects in other organs or tissues
	Systemic distribution	
Intracoronary injection	Direct delivery to the heart	Risk of microvascular obstruction
	Higher retention	Limited to coronary arteries Requires specialized equipment and expertise
	Minimally invasive	
Intramyocardial injection	High local retention	Invasive procedure
	Precise targeting	Limited repeated application
	Potential for enhanced efficacy	Risk of tissue damage

Table 3
Effects and principles of pretreating stem cells with drugs or chemical agents.

Name	Functions	Principles	Ref.
Trimetazidine (TMZ)	Avoiding cell death induced by oxidative stress	Enhance pro-survival factors like HIF-1α, Akt, and Bcl-2	[103–107]
Diazoxide (DZ)		Open/activate mitochondrial ATP-sensitive potassium channels	[106]
Vitamin E		Free radical scavenging ability	[108–110]
Carvedilol		Remove superoxide for antioxidant properties	[133]
2,4-dinitrophenol (DNP)	Chemically induced hypoxia	Inhibition of electron transport chain and reduction of intracellular ATP production to induce chemical hypoxia	[111–113]
Deferoxamine (DFO)		As an iron chelating agent to inhibit prolyl hydroxylase activity to be involved in HIF-1α degradation	[114–116]
Dimethyloxaloylglycine (DMOG)		Proline hydroxylase inhibitors regulate HIF-1α and its phosphorylation under hypoxic conditions	[117–119]
Isoflurane (ISO)		Activate HIF-1α	[120]
Cobalt chloride ($CoCl_2$)		Blocking the HIF-1α degradation, to induce its accumulation	[121–123]
Chemical reprogramming compounds	Induces cell reprogramming to the desired cell type	The substitution of transcription factors by chemical small molecules reverses already differentiated cells into pluripotent cells	[125–128]
Statins	Anti-apoptosis, antioxidant, anti-inflammatory, immune and regenerative ability	Details in Table 3	[130]

Table 4
The statin agents and their effects on the behavior of mesenchymal stem cells (Hydrophilic (H) or lipophilic (L); Y indicates stimulating effect; - indicates lack of data) [130].

Statins	SIM	ATV	LOV	PRA	PTV	RSV	FLV	MEV
H or L	L	L	L	H	L	H	L	L
Differentiation	Y	Y	Y	Y	Y	Y	Y	Y
Cell survival	Y	Y	Y	Y	Y	Y	–	–
Angiogenesis	Y	Y	–	–	Y	Y	–	–
Proliferation	Y	Y	Y	Y	–	–	Y	–
Migration	Y	Y	–	–	–	–	–	–

Annotation: simvastatin (SIM), atorvastatin (ATV), lovastatin (LOV), pravastatin (PRA), pitavastatin (PTV), rosuvastatin (RSV), fluvastatin (FLV), and mevastatin (MEV).

4.3. Engineered stem cells

To target stem cells to damaged areas and retain them within the target tissues, many studies have employed cell surface modifications and genetic engineering to enhance targeted delivery, significantly improving therapeutic outcomes (Fig. 6A). These modifications include attaching specific antibodies, cell adhesion proteins like p-selectin and VCAM-1, platelet nanovesicles (PNVs), and magnetic nanoparticles to the surface of the delivered cells [55]. Additionally, targeting damaged cardiac tissue can be modulated by coupling cells with polymers, electrostatic assembly, or insertion into the lipid bilayer [134].

In vitro genetic modification of stem cells is an effective strategy that regulates the gene expression of interest via non-viral or viral vectors, enhancing cell survival, paracrine factor secretion, and the ability to repair injured myocardium (Fig. 6B) [135]. Gene modification methods for stem cells include controlling the production of their naturally required products (such as pro-inflammatory/anti-inflammatory mediators and cytokines) or enhancing the therapeutic effects of MSCs by introducing key exogenous genes. Additionally, genetic modification can be used to increase the expression of surface receptors [10] or enable the expression of non-native products for specific therapeutic applications [136]. For example, Park et al. encapsulated genetically engineered BMSCs (eBMSCs), which express high levels of hepatocyte growth factor (HGF), within a 3D cardiac patch implanted on the epicardium. In the MI-animal model, HGF secreted by eBMSCs induced long-term enhanced angiogenesis and cell viability in eBMSCs, ultimately promoting angiogenesis and recovering cardiac function in the infarcted heart [137]. Sun et al. genetically modified MSCs to overexpress HIF-1α, which upregulates the VEGF factor via binding to the hypoxia response element (HRE) in the VEGF promoter region. The study investigated the repair of hypoxia-injured human umbilical vein endothelial cells (HUVECs) and the effects on cardiac function in an MI rat model using exosomes derived from HIF-1α-overexpressing MSCs. The results showed that exosome application restored the migration, angiogenesis, and proliferation of hypoxia-injured HUVECs. In the rat MI model, exosomes exerted strong cardioprotective effects by promoting new blood vessel formation in the ischemic border zone [138]. The advantage of this strategy is the sustained long-term effect after initiation. However, the safety of genetically engineered stem cells must also be considered, including the constitutive and unregulated expression of transgenes. Therefore, closely monitoring genetically modified stem cells after transplantation is a critical limitation for future clinical use.

4.4. Utilizing biomaterials as delivery carriers

Because of the low retention and survival rates of directly injected cells, there is growing interest in cell therapy that utilizes biomaterials as cell carriers, as this approach improves the delivery and retention of cells at targeted locations [45,140–142]. Currently, injectable hydrogels and cardiac patches are common methods for utilizing biomaterials to deliver stem cells for cardiac tissue repair. Injectable hydrogels create an optimal environment for cell functions, enabling local delivery via minimally invasive methods. This approach addresses the clinical and surgical challenges of traditional scaffold implantation, enhancing treatment efficiency, patient comfort, and compliance (Fig. 7) [41]. During a myocardial infarction, ECM degradation and massive myocardial cell necrosis lead to a reduction in myocardial wall thickness. According to Laplace's law ($T = (P*R)/t$), myocardial wall tension (T) is directly proportional to intraventricular pressure (P) and the radius of curvature (R), while being inversely proportional to wall thickness (t) [143]. Consequently, increasing wall thickness by injecting fillers like hydrogels can reduce wall stress, lowering ventricular wall stress and supporting cardiac function [144]. Additionally, hydrogels' stiffness and injection volume can affect ventricular wall stress and thickness. Wang et al. created a finite element model using hydrogel injection volumes of 150 μL and 300 μL, evaluating the modulus from 0.1 kPa to 100 kPa (Fig. 8) [145]. The results indicated that larger injection volumes and greater stiffness reduced diastolic myofiber stress by preserving wall thickness during loading. However, the effect diminished when hydrogel injection stiffness reached 50 kPa [145]. The Department of Cardiology at the First Affiliated Hospital of the Air Force Medical University reported the clinical application of transcatheter endocardial injection of alginate hydrogel in patients with chronic heart failure [146]. Six-month postoperative follow-up showed significantly improved cardiac function, increased LVEF, and reduced left ventricular end-diastolic and end-systolic volumes. Thus, injectable hydrogels for intramyocardial delivery hold promise for limiting pathological remodeling after myocardial infarction. However, there are many challenges, such as significant differences in hydrogel injection timing

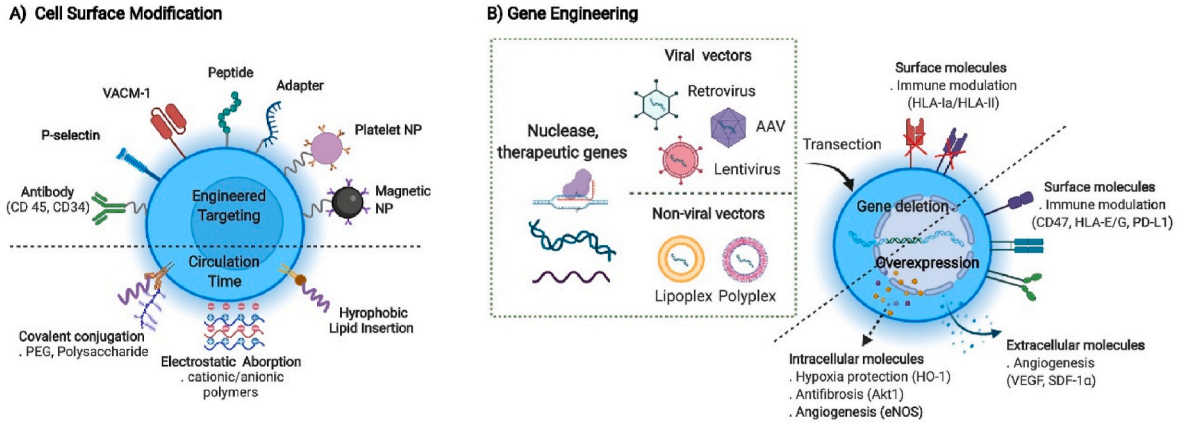

Fig. 6. Engineered stem cells to improve therapeutic efficiency. (A) Modifications on the cell surface. (B) Genetic engineering [139]. Copyright 2021, Elsevier.

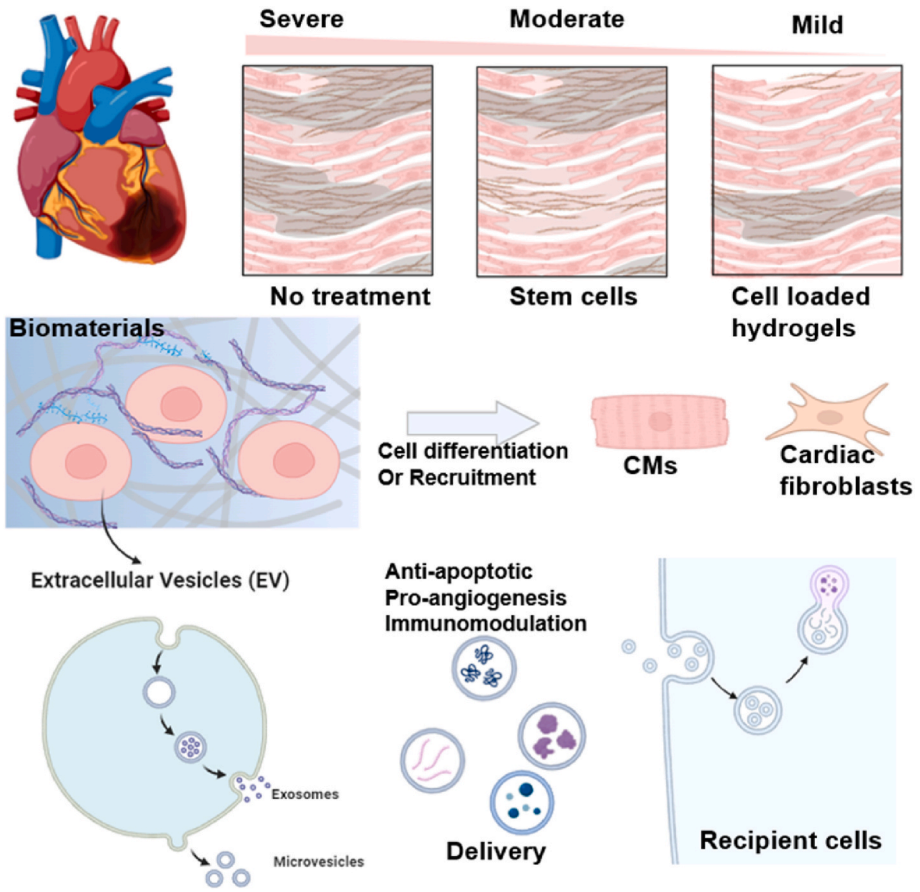

Fig. 7. Mechanism of stem cell-laden hydrogel used in myocardial repair. Exogenous inducible factors can increase the potential differentiation of stem cells into CMs by modulating the modulus. Due to the paracrine effects, stem cells also inhibit CMs' apoptosis and promote angiogenesis and immune regulation by releasing exosomes in infarcted sites. Created by Biorender.

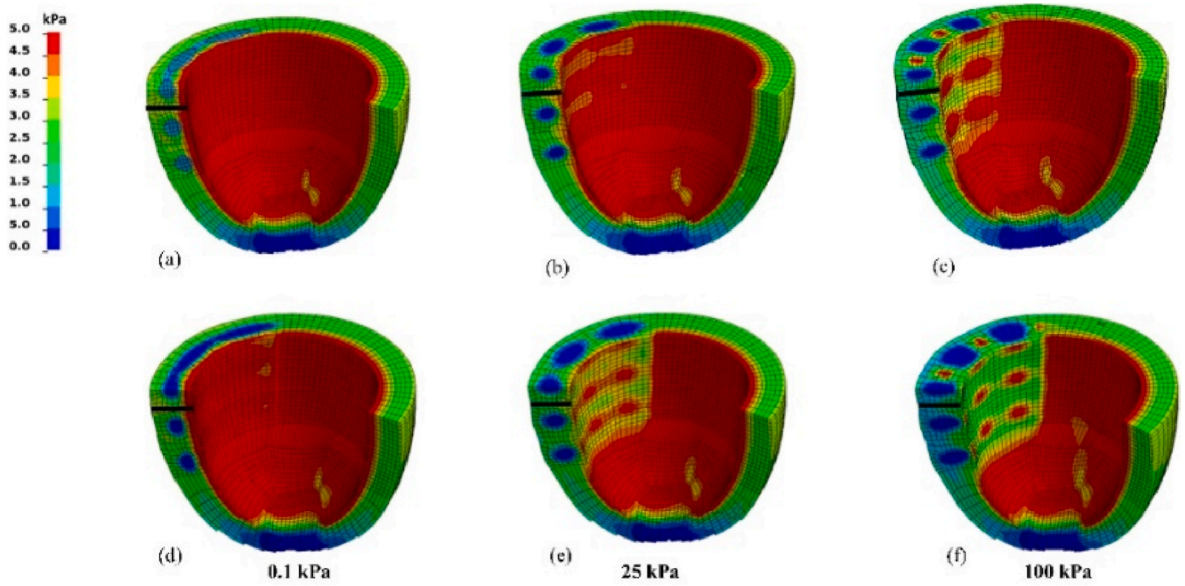

Fig. 8. Stress distribution in left ventricular end-diastolic muscle fibers following hydrogel injection. (a–c) was injected with 150 μL, (d–f) was injected with 300 μL, and the stiffness values were 0.1 kPa, 25 kPa, and 100 kPa, respectively. Copyright 2017, Elsevier [145].

and volume, material types and their properties, and outcome measurements [143]. In preclinical trials, injectable hydrogels have been utilized to deliver different cell types to the heart, improving cell retention rates and enhancing cardiac repair. Results indicate that biomaterials enhance the retention and localization of delivered cells compared to saline, with the improvement in cell retention becoming more pronounced over time [147,148]. Additionally, hydrogels can modify the microenvironment of myocardial infarction (MI) to enhance

the survival conditions of encapsulated cells, thereby influencing their viability and fate [45]. For example, hydrogels can shield cells from ischemia and inflammation while preventing apoptosis [20]. The appropriate mechanical and flow properties of injectable hydrogels help protect cells during injection [144,149,150].

Although injectable hydrogels are widely used for myocardial repair, intracardiac injection may cause tissue damage. To overcome this limitation, cardiac patches have been developed for local delivery of stem cells or bioactive molecules to the site of MI. The patches feature unique designs and structures, such as cell patterns, microneedles, and adaptive patches (Fig. 9A) [151,152]. It provides physical support to the weakened heart muscle (mechanical structural support) while also actively guiding the differentiation of implanted human embryonic stem cells into functional cardiomyocytes (heart muscle cells), ultimately improving the heart's pumping ability by replacing damaged tissue with newly formed, contractile cells [85]. However, a major hurdle in using heart patches clinically is achieving the appropriate size and thickness to match a human heart attack while also ensuring sufficient blood vessel growth (vascularization) within the patch to maintain the viability of the implanted cells, as larger patches face challenges with oxygen and nutrient delivery to deeper tissue layers [86]. Vascularization of the patch can be achieved through several strategies including direct 3D printing, co-culture, and bionic microvessels (Fig. 9B) [152,153]. In addition, the structure of the patch needs to be considered to match the heart. Otherwise, it can lead to serious adverse remodeling and deterioration [154]. Once implanted, the heart patch is stretched according to the heart movement; to achieve the higher adaptability of the heart patch, the 4D patch has the anisotropic arrangement of the human heart from dynamically stretching, preventing the material from deforming during the transition between the diastolic and systolic periods [155].

4.5. Adjustment of MI tissue microenvironment by biomaterials

Complex pathological changes occur after myocardial infarction, showing pathological features such as ischemia and inflammation and releasing related oxidative stress and harmful cytokines, leading to the death of implanted cells. When entering the proliferative phase and myocardial function declines, the implanted cells may be disturbed by myofibroblasts. In the fibrotic environment, the increase of collagen tissue stiffness inhibits cell migration, structural maturation of transplanted cells, and vascularization for tissue repair (Fig. 10). Therefore, to increase the cell therapeutic efficacy, researchers tried to improve stem cell survival in vivo by modifying the MI pathological microenvironment.

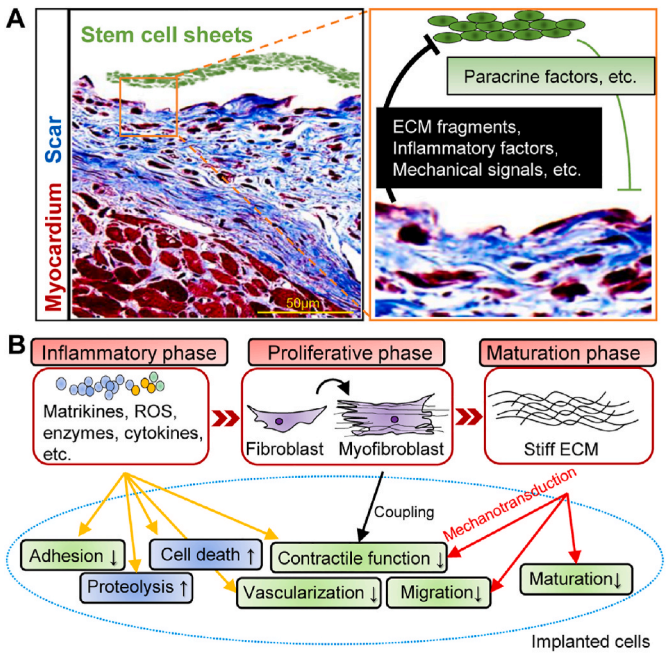

Fig. 10. Effect of MI microenvironment on implanted cells [11]. Copyright 2019, The Authors.

Modulating the MI tissue microenvironment through biomaterials is one of the strategies to achieve successful stem cell transplantation. Biomaterials can reproduce the microenvironment of stem cells and create a favorable microenvironment around MI tissues [20]. Biomaterials assist in adding components, such as cytokines, growth factors, and immunomodulators, to promote the repair of the MI tissue microenvironment to extend its residence time at the stem cell transplant site [156]. At the same time, the temporal control and release kinetics of bioactive factors are considered according to the required stage of treatment. Li et al. fabricated a hydrogel with bFGF and ROS response (Gel-bFGF) and delivered it directly into the pericardium. ROS-sensitive crosslinked polyvinyl alcohol (PVA) hydrogels carry bFGF and decompress ROS, releasing bFGF into the heart tissue in an "on-demand" way [157]. Hao et al. designed a dual-function hydrogel that clears ROS and releases NO with a borate-protected diazodiol ester (CS-B-NO). CS-B-NO hydrogel can inhibit oxidative stress and inflammation by intracardial injection of ROS/NO imbalance after myocardial

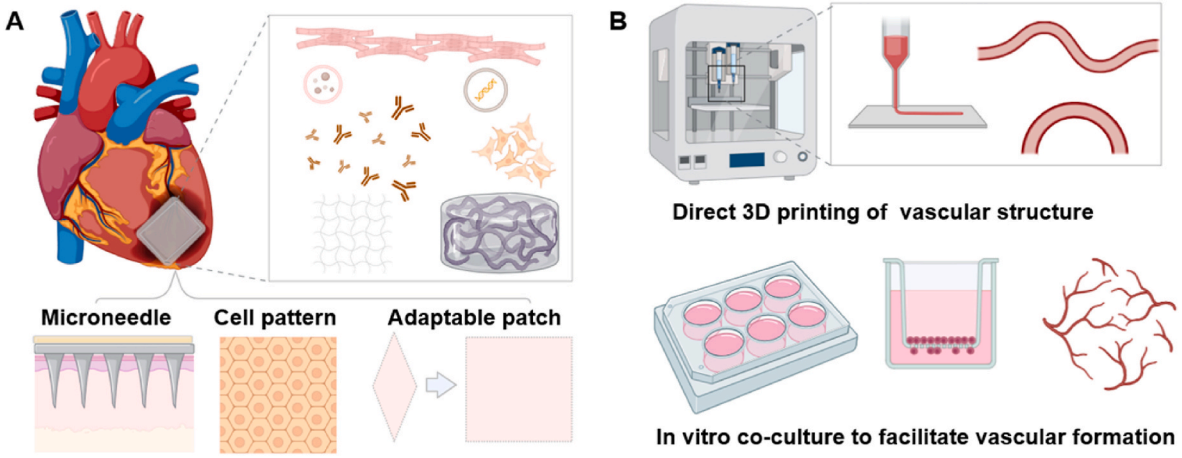

Fig. 9. The heart patch comprises cells, bioactive molecules, and biomaterials. (A) Patches with different designs and structures include cell patterning, microneedles, and adaptable patches. (B) The vascularization of the patch is essential for the function of the cells therein. Different strategies can achieve vascularization, including 3D printing, co-culture, and biomimetic microvessels. Created by Biorender.

injury [158]. Zhou et al. developed a hydrogel of natural melanin nanoparticles (MNPs) and alginate (MNPs/Alg) by cross-linking with calcium ions. This hydrogel modulates oxidative stress and influences macrophage phenotype in the myocardium, thereby facilitating myocardial repair [159]. Li et al. designed an injectable hydrogel with MSN/miRNA complex, demonstrating a synergistic effect of inflammation inhibition and angiogenic enhancement in MI treatment. The principle of this drug delivery system is that the pH in situ can trigger the release of MSN/miRNA complex from the hydrogel, which enters the cell to deliver the MSN/miRNA complex from the hydrogel on demand [160]. An et al. proposed a strategy for treating MI using MSC spheroids coated with a self-assembling protein/polyphenol armor. This innovative approach significantly improved therapeutic effectiveness by actively addressing the challenging MI microenvironment. It provided multiple benefits, including shielding donor cells from immune clearance, remodeling the ROS microenvironment, and enhancing the healing paracrine secretion of MSCs [161]. Le et al. prepared microscale microrods based on hyaluronic acid (HA) to provide local biochemical and biomechanical signals affecting cell fate. In an ischemia-reperfusion model of myocardial infarction rats, this micromechanical interaction mitigated the fibrosis phenotype and improved morphological and functional outcomes [162]. Furthermore, the capacity of biomaterials to minimize fibrosis and establish an immune-isolating environment is essential for enhancing both acute and long-term outcomes of stem cell transplants [163]. By adjusting biophysical and chemical properties—such as strength, hydrophilicity, morphology, surface charge, and porosity—biomaterial-protein adsorption and biomaterial-cell interactions can be managed to promote positive immune responses [164, 165].

5. Conclusion

Myocardial infarction (MI) is the most prevalent type of acute heart injury that can result in heart failure. MI resulting from different types of injury can activate intricate healing processes to restore heart function. Although collagen deposition is a normal and essential aspect of wound healing, it can lead to a progressively irreversible fibrotic response. Myocardial fibrosis is the excessive accumulation of collagen after heart injury, causing cardiac dysfunction, resulting in an increased incidence of arrhythmia and sudden cardiac death, and becoming a primary reason for the progression of heart failure. Given the limited regenerative ability of mature cardiomyocytes, stem cell therapy presents an innovative treatment option for many patients with heart injuries. Previous experimental studies and various clinical trials have shown the safety and feasibility of this approach. Nonetheless, numerous challenges remain in the field of stem cell therapy.

Currently, stem cells can be delivered to the body in various ways, with most being excreted directly from the heart due to off-target and low localized retention, transferred from the injection site via lymphatic/vascular channels, or dying at the injection site. Recently, various methods, such as blocking the injection site to prevent cell backflow, overexpression of cell surface receptors, and physical and chemical methods for cell pretreatment, have been developed to enhance cell retention (Table 5). However, there are problems: 1) The immune response identifies and clears transplanted cells. A variety of factors from immune cells are detrimental to transplanted cells; 2) Decreased pH, increased MMP, and excess ROS in infarct area could lead to apoptosis of transplanted cells; 3) The lack of ECM microenvironment basis, insufficient blood supply, and hypoxia in the infarction area could not support cell survival. Therefore, increasing the cell retention and targeting rate is a prerequisite to improving the efficacy of stem cell therapy. In addition, reducing the influence of pathological microenvironments on stem cells after myocardial injury is still a challenge. And the exact mechanism by which stem cells repair damaged hearts is still completely unknown.

Finally, the prospects were proposed to develop novel stem cell therapeutic strategies for efficient treatment of MI. 1) Combining Artificial Intelligence (AI) tools to analyze information from extensive datasets creates models that provide a robust strategy for developing stem cell therapies. For example, AI tools analyze single-cell RNA sequencing (scRNA-seq) data to identify optimal stem cell subtypes with cardioprotective, regenerative, or immunomodulatory potential. 2) Combining multiple strategies, such as gene editing with hydrogel delivery or magnetic targeting, has shown the most promise in enhancing cell homing and retention in the infarcted myocardium. 3) Design of innovative biomaterials to improve stem cell delivery, retention, and survival in the infarcted heart. Specifically, the pathogenesis of MI and the rational design of innovative biomaterial to regulate the microenvironment and guide the immune cells' behavior as a synergistic strategy to support stem cells for myocardial repair.

Table 5
Summary of strategies to enhance MSC efficacy for cardiac repair.

Strategy	Approaches	Advantages	Disadvantages
Chemokine-BasedHoming	SDF-1/CXCR4 signaling	✓ Enhanced stem cell migration	✓ The short half-life of chemokines ✓ Risk of off-target effects
Surface Engineering	Coating with ligands or nanoparticles	✓ Improved adhesion and specificity ✓ Improves engraftment	✓ Temporary modifications
Genetic Engineering	Overexpression of homing/ survival genes	✓ Targeting and functional integration	✓ Risk of genetic instability ✓ Complex and costly processes
Biomaterial Delivery	Hydrogels/ Cardiac patches	✓ Enhanced retention and survival ✓ Protects cells from apoptosis	✓ Complex material design and delivery logistics ✓ Risk of immune rejection
Exosome-Based Strategy	Modified stem cell-derived EVs	✓ Cell-free therapy and targeted delivery	✓ Limited effects due to short duration
MagneticTargeting	Magnetic particles and magnetic field	✓ Precision homing with magnetic field	✓ Risk of magnetic particle toxicity ✓ Limited clinical validation
Preconditioning	Hypoxia, cytokine, or drug pretreatment	✓ Increases cell survival and homing efficiency ✓ Enhances paracrine	✓ Time-sensitive protocols ✓ Limited effects due to short duration
Cell-Sheet Engineering	Cell-layer transplantation	✓ Improved engraftment and paracrine effects	✓ Complex and time-consuming processes ✓ The cell sheets prone to fragmentation

CRediT authorship contribution statement

Chuanfeng An: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Investigation, Formal analysis, Data curation, Conceptualization. **Yuan Zhao:** Validation, Software, Resources, Investigation, Funding acquisition, Conceptualization. **Lipeng Guo:** Resources, Methodology, Formal analysis, Data curation. **Zhijian Zhang:** Software, Methodology, Formal analysis, Data curation, Conceptualization. **Chunxiao Yan:** Validation, Software, Methodology, Data curation. **Shiying Zhang:** Visualization, Validation, Software, Data curation, Conceptualization. **Yujie Zhang:**

Visualization, Software, Resources, Data curation. **Fei Shao:** Software, Resources, Methodology, Data curation. **Yuanyuan Qi:** Visualization, Software, Methodology, Data curation. **Xun wang:** Software, Resources, Methodology, Investigation, Formal analysis, Data curation. **Huanan Wang:** Writing – review & editing, Validation, Supervision, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Lijun Zhang:** Writing – review & editing, Supervision, Project administration, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

Data will be made available on request.

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