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Hydrogel-based cardiac repair and regeneration function in the treatment of myocardial infarction

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ABSTRACT

A life-threatening illness that poses a serious threat to human health is myocardial infarction. It may result in a significant number of myocardial cells dying, dilated left ventricles, dysfunctional heart function, and ultimately cardiac failure. Based on the development of emerging biomaterials and the lack of clinical treatment methods and cardiac donors for myocardial infarction, hydrogels with good compatibility have been gradually applied to the treatment of myocardial infarction. Specifically, based on the three processes of pathophysiology of myocardial infarction, we summarized various types of hydrogels designed for myocardial tissue engineering in recent years, including natural hydrogels, intelligent hydrogels, growth factors, stem cells, and microRNA-loaded hydrogels. In addition, we also describe the heart patch and preparation techniques that promote the repair of MI heart function. Although most of these hydrogels are still in the preclinical research stage and lack of clinical trials, they have great potential for further application in the future. It is expected that this review will improve our knowledge of and offer fresh approaches to treating myocardial infarction.

1. Introduction

Atherosclerosis (AS), heart failure (HF), myocardial infarction (MI), coronary heart disease (CHD), etc. are examples of cardiovascular disease (CVD), a category of diseases that affect the heart and blood arteries and often have a high mortality rate. MI, in particular, refers to a condition where severe ischemia and hypoxia occur in the heart tissue due to reduced or blocked blood flow in the coronary arteries, leading to a significant loss of cardiomyocytes as a result of an exacerbated inflammatory response [1,2]. Myocardial infarction, commonly known as a heart attack, is a leading cause of death globally, posing a significant challenge to public health worldwide [3–5]. A study in Korea showed that the incidence of MI hospitalizations increased from 71/100,000 per year to 100/100,000 per year between 2011 and 2018, and is still on the rise [6]. Currently, the available treatment methods for MI can only improve cardiac function to a certain extent and cannot fully compensate for the loss of cardiomyocytes, which ultimately leads to an energy supply imbalance in cardiac muscle cells, contributing to heart failure. Consequently, in order to effectively treat MI clinically, new treatment approaches must be developed (see Table 1).

Hydrogel is a kind of polymer with three-dimensional network structure formed by crosslinking of polymer backbone and hydrophilic functional groups through covalent bonds, ionic bonds, hydrogen bonds or physical entanglement [7]. Depending on their origin, hydrogels can be categorized as either natural or synthetic. Natural hydrogels include alginate, acellular extracellular matrix, chitosan and so on. Synthetic hydrogels include polyacrylic acid and its derivatives, polyvinyl alcohol, peptides, etc [8]. The network structure formed in this way is stable and

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Table 1
Summarization of common intelligent responsive hydrogels.

Intelligent hydrogel type	Hydrogel host molecules	Hydrogel function	Ref.
Temperature responsive hydrogel	PNIPAAm、PEG-PLGA、PVCL、Dex-PCL-HEMA	For the purpose of giving the myocardium mechanical support, it is in a liquid form at ambient temperature and solidified into a gel state at 37 °C.	[29–33, 39]
PH responsive hydrogel	NIPAAm-co-PAA-co-MA-PEG-co-HEMA-oTMC	The main chain of the hydrogel polymer contains carboxyl groups, which maintains the molecular form in the acidic environment (PH < 6.8) of the infarct area and forms a delivery system.	[42,43, 45]
ROS-responsive hydrogel	AMB-G-TK/4-arm-PEG-SG、HA-MA、PAAc、NO-RIG	It has antioxidant properties, effectively promotes tissue recovery, eliminates excessive ROS, and reduces myocardial tissue inflammation.	[46,47, 49,60, 63]
Conductive responsive hydrogel	PAN/LS、PAMB、PPy、CNFs、collagen/ADH-CNCs/CS-Au	Encourage the formation of a functioning syncytium from cardiomyocytes and restore its electrical function.	[71,81, 88,99, 100]
Magnetic responsive hydrogel	SPIO、MNPs	Accurate magnetic stimulation of the vagus nerve can rapidly improve MI heart repair.	[83,98]

has higher strength. As an ideal tissue engineering repair material, hydrogel has the following advantages compared with other materials [9–12]: high water content, good biocompatibility, and low possibility of

immune response with the host; there is an appropriate degradation rate in the body, about equal to the heart tissue regeneration rate; excellent mechanical qualities preserve heart function while giving the infarct area physical support; after injection into the body, there is a suitable sol-gel phase transition time, slow or fast phase transition time is unfavorable to the myocardium. The hydrogel creates a new kind of in vivo drug delivery system (DDS) as a carrier for the local release of active cytokines, cells, and medications as a result of its outstanding advantages. Different types of injectable hydrogels demonstrate substantial potential in myocardial repair and regeneration of MI, and achieve the superposition of multiple therapeutic effects [13,14]. It has been proved to improve the survival rate and prognosis of MI, which offers a wide-ranging perspective for diagnosing and cure of MI.

This paper investigates the utilization of hydrogels in the treatment of MI as illustrated in Fig. 1. In the treatment strategy, we introduced the design process of different hydrogels including natural hydrogels and responsive hydrogels, and various loaded hydrogels containing stem cells, bioactive factors, miRNAs, etc., and the application reports in MI animal models. Given the limited number of reports on the use of cardiac patches in animal models of myocardial infarction, we will focus on the latest progress in how to target the MI area and restore cardiac function. Finally, we reviewed the new biomolecular delivery system of hydrogels in the treatment of MI, and discussed the rapid development of hydrogels as a new type of biomaterial that requires a strict clinical regulatory model. At the same time, hydrogels also need to overcome many difficulties from laboratory to clinical, which requires researchers to work together to solve. Nonetheless, with our comprehensive exploration of

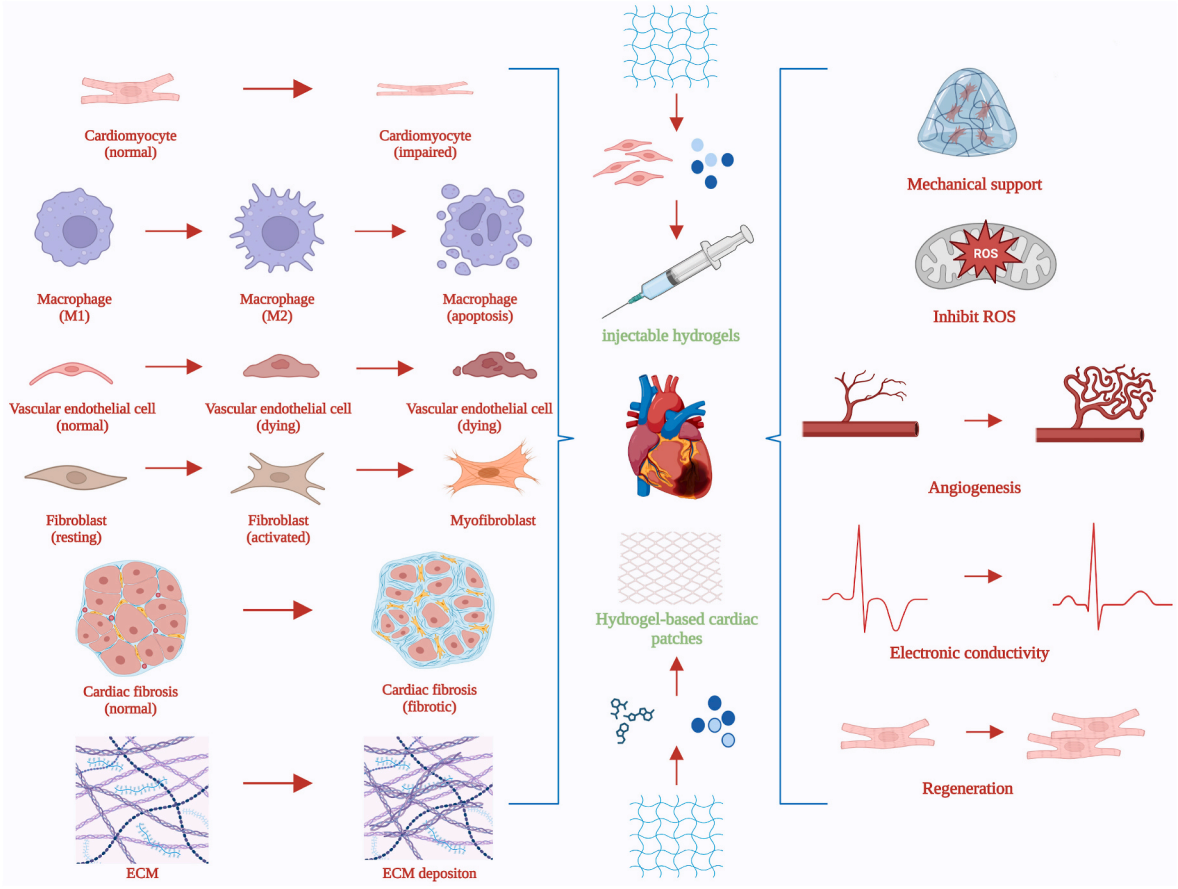

Fig. 1. Diagram of the pathological process of myocardial infarction and the repair of cardiac function by hydrogel and cardiac patch. Created with BioRender.com.

the pathophysiology of myocardial infarction and the intricacies of hydrogel therapy, targeting the myocardial infarction location in vivo with hydrogel may be a promising future.

2. Hydrogels for cardiac tissue engineering

Currently, treatment methods for myocardial infarction are continuously evolving; however, the restoration of cardiac function after myocardial infarction remains the focus of treatment. Conventional drug delivery methods face challenges such as repeated administration and systemic toxicity. Therefore, there is a constant need to refine drug delivery approaches. Injectable hydrogels represent a category of hydrophilic three-dimensional polymer networks that enter the body in liquid form and, under specific conditions, transform into a gel state. They provide support to the damaged myocardium, reduce ventricular wall stress, and inhibit ventricular remodeling. These biomaterials can be injected alone or serve as carriers for cells or other bioactive substances, applied to myocardial infarction, and demonstrate excellent performance in improving post-infarction cardiac function and reducing infarct size.

Natural materials extracted from living organisms, consisting of proteins (such as collagen, fibrin, gelatin, keratin, fibroin and silk protein) or polysaccharides (such as alginate, hyaluronic acid, agarose, chitosan, etc.), have been shown to preserve good biochemical and biological properties and improve biocompatibility with host tissues. It has high bioactivity, biocompatibility and degradability. The unique absorption properties of natural injectable hydrogels enable the exchange of nutrients and metabolites through scaffolds, thereby improving cell survival and mobility into surrounding tissues, reducing wall stress. Leveraging the advantages of natural hydrogels, there have been treatment cases applied to myocardial infarction. Leor et al. [15] confirmed that the injection of biodegradable alginate solution into the infarcted myocardium can stimulate the formation of new blood vessels and effectively reduce the expansion of the infarcted area of the heart. Based on the aforementioned studies, it is easy to conclude that acellular extracellular matrix hydrogel has a high biocompatibility and immunogenicity, removes immunogenic cells through acellular technology, provides mechanical support, fixation, and structural protection for the myocardium in vivo, and maintains homeostasis of the internal environment. This material has great potential for clinical transformation of the treatment of myocardial infarction. Sources of dECM are abundant and relatively easy to obtain. Zhi Qing ‘s team [16] found that the extracellular matrix of decellularized small intestinal submucosa improved the microenvironment of tissue repair after infarction. In the infarcted lesion, the expression of myocardial stem cell factor was significantly increased, which promoted the migration of C-Kit positive cells and macrophages in the myocardium of rats with ischemia-reperfusion injury, and improved cardiac function and poor cardiac remodeling.

Natural hydrogels successfully restored heart function, suppressed ventricular remodeling, and lowered the inflammatory response in an animal model of myocardial infarction, laying the groundwork for eventual clinical studies. Currently, two alginate-based hydrogels (Algisyl-LVR and IK-5001) have successfully entered the clinical trial stage. The results of phase II clinical study of AUGMENT-HF [17] showed that compared with conventional drugs combined with surgical treatment, Algisyl-LVR by epicardial injection significantly increased the peak oxygen uptake and improved cardiac function in patients with advanced heart failure for 12 months, and the use of Algisyl-LVR did not introduce other clinical safety issues. Based on the above basis, a larger clinical trial of Algisyl-LVR has been successfully opened to further evaluate its safety and efficacy. In the RESERVATION-1 study [18], IK-5001 was injected into the coronary artery through a catheter. Through the damaged capillaries after infarction, it became gelatinous in a local high calcium environment and became a degradable extracellular matrix during infarction. It provides support to the damaged area of the myocardium and reduces wall stress. Clinical results showed that IK-5001 exhibited excellent safety and significantly improved exercise tolerance in MI patients.

In view of the safety of Algisyl-LVR in clinical trials conducted abroad, China Deke Medical Co., Ltd. improved Algisyl-LVR and developed a new type of hydrogel. The clinical safety and feasibility of alginate hydrogels for the treatment of patients with heart failure were verified for the first time in China (NCT04781660). Existing small-sample data showed that the hydrogel dramatically improved the left ventricular ejection fraction of patients and significantly improved cardiac function.

In addition, the cellular ECM has been demonstrated to be practical and potentially useful as an injectable scaffold for cardiovascular tissue engineering. VentriGel hydrogel is a kind of extracellular matrix extracted from porcine cardiomyocytes. Phase I clinical trials have been conducted in the United States [19]. Fifteen patients with left ventricular dysfunction after MI were included in a phase I clinical trial of the VentriGel hydrogel. Six months after the endocardial injection of VentriGel, the patients were followed-up. The clinical results of MI patients with intracardiac injection of VentriGel showed that the hydrogel was safe and feasible, and for patients with a history of MI for more than one year, it significantly increased the left ventricular end-systolic volume at three and six months after intramyocardial injection. After receiving approval from the US Food and Drug Administration, a VentriGel phase II clinical study was formally initiated based on the findings of phase I clinical studies.

Unfortunately, natural hydrogels suffer from significant batch variations, poor mechanical properties, and potential immunogenicity issues. Consequently, researchers have addressed these challenges by refining manufacturing processes and developing various types of synthetic hydrogels. This category of hydrogels effectively compensates for the mechanical strength, degradation rate, and other performance limitations associated with natural hydrogels. Furthermore, it enables the loading of therapeutic drugs, bioactive factors, transplantable stem cells, and relevant RNA into the hydrogel, imparting multiple functionalities to facilitate a synergistic effect in the treatment of myocardial infarction.

3. Pathophysiological process of myocardial infarction

Myocardial infarction comprises three primary stages: inflammation, proliferation, and remodeling. During the inflammatory phase of myocardial infarction, cardiomyocytes undergo cell death, leading to the release of pro-inflammatory factors that trigger the cleavage of the extracellular matrix (ECM). At this time, a large number of cardiomyocytes lose their normal cellular function. The production of NF-κB-dependent cytokines and chemokines is upregulated in damaged cells, and a high number of neutrophils are drawn to the site of MI. The monocytes subsequently undergo macrophage differentiation, transform into macrophages, consume ECM fragments and dead cardiomyocytes, and release growth factors that stimulate angiogenesis. Macrophages are beneficial for inhibiting inflammatory response and neutrophil degradation. In the proliferative phase, as the inflammation subsides, the injured myocardial area accumulates numerous fibroblasts, which transform into myofibroblasts. These myofibroblasts initiate the synthesis of extensive ECM. As cardiac wall pressure increases, ECM production was dramatically improved. Following a few weeks, collagen fibers started to develop all throughout the infarct region, taking the place of the deceased myocardial cells. Notably, different matrix metalloproteinases and tissue inhibitors of metalloproteinases are produced and altering the extracellular matrix, and scarring of the myocardium’s injured regions eventually contributes to cardiac remodeling [14].

The pathological progression of myocardial infarction is a gradual process, and it is essential for researchers to design and implement effective treatment strategies based on the specific stage of the pathology. Providing accurate treatment to MI patients is of utmost

importance. During the initial inflammation stage, cardiomyocytes die due to ischemia and hypoxia, and subsequently inflammatory cells and neutrophils accumulate in the infarct area, promoting the lysis of ECM. Therefore, practical biomaterials for this first stage should be capable of stimulating cardiomyocyte activity, preventing apoptosis, and preserving ECM integrity. Besides, in the first stage, reducing the amount of white blood cells, reducing acute inflammation, and inhibiting the distribution of inflammatory substances are necessary because the long-term inflammatory response increases the development of cardiac fibrosis and heart rupture [20]. Endothelial and fibroblasts grow during MI proliferation, a process closely associated with angiogenesis, myofibroblast differentiation, and collagen deposition. Biomaterials designed for this stage should focus on regulating macrophage phenotype and behavior, influencing fibroblast activity, and facilitating blood vessel development [21]. In the final remodeling stage, scars rich in over-crosslinked collagen eventually replace dead cardiomyocytes, further affecting normal myocardial function. Cardiomyocytes or cardiac tissue from the infarct region should be replaced at this point with foreign regenerative cells or synthetic biomaterials that resemble myocardial tissue [22].

In summary, hydrogel serves as a novel in vivo delivery system for repairing myocardial infarction through the following mechanisms: (1) By increasing the thickness of the ventricular wall in the infarction area, it provides mechanical support, creates conditions for endogenous repair, and improves the microenvironment. (2) As a control release carrier of proteins or growth factors, prevent these bioactive molecules from being degraded by enzymes in the body, extend their action time in the body, and achieve local drug delivery. (3) As a carrier for cell transplantation, it can prevent cell escape caused by heart beating and venous return through its own viscosity, improve the retention of transplanted cells, provide a suitable three-dimensional growth environment for transplanted cells, prevent cell apoptosis, and improve the survival rate of transplanted cells.

4. Hydrogels for treating MI during the inflammation phase

Inflammation is a complex biological response of the body to a variety of harmful stimuli. While eliminating cell damage and promoting tissue repair, it inevitably leads to further damage. In the early stage of myocardial infarction, a robust inflammatory response occurs, releasing pro-inflammatory factors. Notable characteristics of the changes in the inflammatory microenvironment within the infarcted area of the myocardium include a weakly acidic environment and an excessive release of reactive oxygen species. These changes can further damage the myocardial muscle, ultimately causing the loss of normal electrical conductivity and other functions in the surviving myocardium, thereby accelerating the pathogenesis of myocardial infarction.

Therefore, biomaterials designed for the initial stage of myocardial infarction should have the capacity to enhance the microenvironment of cardiomyocytes. They should promote cardiomyocyte activity, reduce cell apoptosis and inflammatory responses, inhibit the expansion of the infarcted area, and provide physical and mechanical support for the damaged myocardium. This support should aid in the restoration of normal physiological functions, including electrophysiological conduction. In this section, we will focus on responsive hydrogels designed according to changes in the microenvironment after myocardial infarction.

4.1. Responsive hydrogel

Intelligent hydrogels are defined as the framework of polymer three-dimensional network structure. According to the physical and chemical changes of the microenvironment in the body, the internal structure of the gel changes, and then the swelling-contraction or gel-sol phase transition occurs. In recent years, intelligent hydrogels have garnered increasing attention. Unlike traditional hydrogels, intelligent hydrogels have certain sensitivity in space and time. Modifying functional groups with specific responsiveness in hydrogel structure is the main method to engender stimulus responsiveness in injectable hydrogels. It has been reported in the literature that intelligent hydrogels that respond to biochemical signals [23–25] (including temperature, PH, ROS, etc.), electromagnetic energy [26] and physical stimuli [27] (including single and multiple types of stimuli) have a good effect in the treatment of myocardial infarction inflammation.

When contacted with human blood and tissue, responsive hydrogels have certain biocompatibility and are easy to be degraded. They have been extensively employed as drug transporters, sustained release agents, and wound adhesives in biomedicine, tissue from human engineering, and other domains. This section is dedicated to highlighting the recent advancements in the application of various responsive injectable hydrogels for myocardial repair.

4.1.1. Temperature responsive hydrogel

The initial stage following MI results in inflammation and activates a number of extracellular signal transduction pathways, which are linked to the remodeling. Temperature-responsive injectable hydrogels are intelligent polymer gels that are sensitive to temperature changes in the body. When the injectable hydrogel enters the body, a solid-liquid two-phase transition can occur with the temperature change of the site; that is, it is in a liquid state when the ambient temperature is below the lowest critical phase transition temperature (LCST), and in a semi-solid gel state when the ambient temperature is higher than the LCST [28]. In other words, the hydrogel can be directly injected into the target tissue and quickly form local gel under the induction of body temperature to provide support for the damaged myocardium. Using the local injection, slow release and non-toxic characteristics of a temperature-sensitive hydrogel as a carrier, it is injected into the site of myocardial infarction to effectively inhibit apoptosis and tissue fibrosis, reduce the infarct size, alleviate the inflammatory response of macrophages and other infiltrating cells, and repair cardiac function to achieve the purpose of treat myocardial infarction.

The LCST of the temperature-sensitive hydrogel based on the amphiphilic polymer polyethylene glycol (PEG)-poly (N-isopropylacrylMIde) (PNIPAAm) is about 37 °C. When the hydrogel is at a temperature higher than LCST, the molecular configuration changes, and the water molecules are forced to leave the polymer skeleton, and the intramolecular hydrogen bonding force is enhanced [29,30]. Based on the temperature sensitivity and good biocompatibility of PNIPAAm, it is frequently utilized in cardiac tissue engineering [31]. In addition to PNIPAAm, there are other copolymer materials, such as PLGA-PEG-PLGA [32] and poly (n-vinylcaprolactam) (PVCL) [33], which have shown great application prospects in biomedicine.

In the early stages of myocardial infarction, a large number of inflammatory cells are recruited to the infarcted area, secreting various inflammatory mediators that have a profoundly adverse impact on cardiac function recovery. Therefore, in the early inflammatory stage following myocardial infarction, the use of anti-inflammatory drugs may be a crucial step. Triptolide (TPL), isolated from the Chinese herb Tripterygium wilfordii, is a compound known for its anti-inflammatory, anti-tumor, and immunomodulatory properties. Wen et al. [34] discovered that TPL has the ability to inhibit NF-κB activity, significantly attenuating cardiac inflammation and improving left ventricular function in diabetic myocardial patients, suggesting its promising therapeutic role in cardiovascular diseases. Unfortunately, systemic administration of TPL can cause hepatotoxicity and nephrotoxicity, and its poor water solubility and low bioavailability severely limit its clinical application. Faced with these challenges, the development of new TPL formulations is needed to achieve therapeutic goals in cardiovascular treatment. Polylactic-co-glycolic acid (PLGA) is a biodegradable copolymer approved by the United States Food and Drug Administration (FDA). PLGA can be utilized for drug encapsulation, enhancing drug bioavailability in vivo, and sustaining drug release [35]. However, PLGA

has a significant drawback in causing a burst release of the drug, potentially leading to severe local toxicity due to a momentary surge in drug concentration. With the continuous development of biomaterial technology, hydrogels can serve as carriers for sustained drug release in myocardial tissue repair. Therefore, it has been hypothesized that combining hydrogels with PLGA nanoparticles may address the release drawbacks associated with PLGA nanoparticles. The PEO-PPO-PEO triblock copolymer constitutes Pluronic F127, which has received clinical practice approval from the FDA. PEO-PPO-PEO, as a thermosensitive hydrogel, transitions to a gel state at body temperature and remains in a liquid state at lower temperatures outside the body, facilitating extracorporeal injection. Research has indicated [36] that drugs loaded into F127 hydrogels can be slowly released within 4 days, effectively preventing the instantaneous burst release observed with PLGA nanoparticles. Building upon this, Kun Wang et al. [37] developed a combination of F127 hydrogel and PLGA nanoparticles, representing a potentially effective therapeutic strategy for delivering TPL to the infarcted area (Fig. 2A). In a rat model of myocardial infarction, TPL-loaded hydrogel (100 μL) was injected into the myocardium 30 min post-surgery. In this study, it was observed that rats receiving the hydrogel injection exhibited reduced TNF-α levels and increased IL-10 levels in the infarcted myocardium, effectively suppressing inflammation in the infarcted area, reducing myocardial cell apoptosis, inhibiting myocardial fibrosis, and improving cardiac function. Temperature-responsive chitosan hydrogel has been proved to be a suitable mechanism for stem cell transplantation. Chitosan hydrogel and nuclear transfer of embryonic stem cells (NTES) were injected into the rat infarct model as a scaffold for the left ventricular wall. The results showed that the hydrogel had the potential to improve the function of infarcted heart and had broad application prospects [38].

Ying Wen et al. [23] injected dextran-poly (ε-caprolactone)-2-hydroxyethyl methacrylate-poly (n-isopropylacrylMIde) (DPHP) hydrogel into the myocardial infarction area of rats after coronary artery ligation, and PBS was used as the control group. After 12 weeks, a histopathological examination was performed to determine the relevant data. The findings demonstrated that DPHP hydrogel could minimize the infarct area and weaken left ventricular remodeling while inhibiting reactive fibrosis and hypertrophy of the myocardium in the distal area. It could

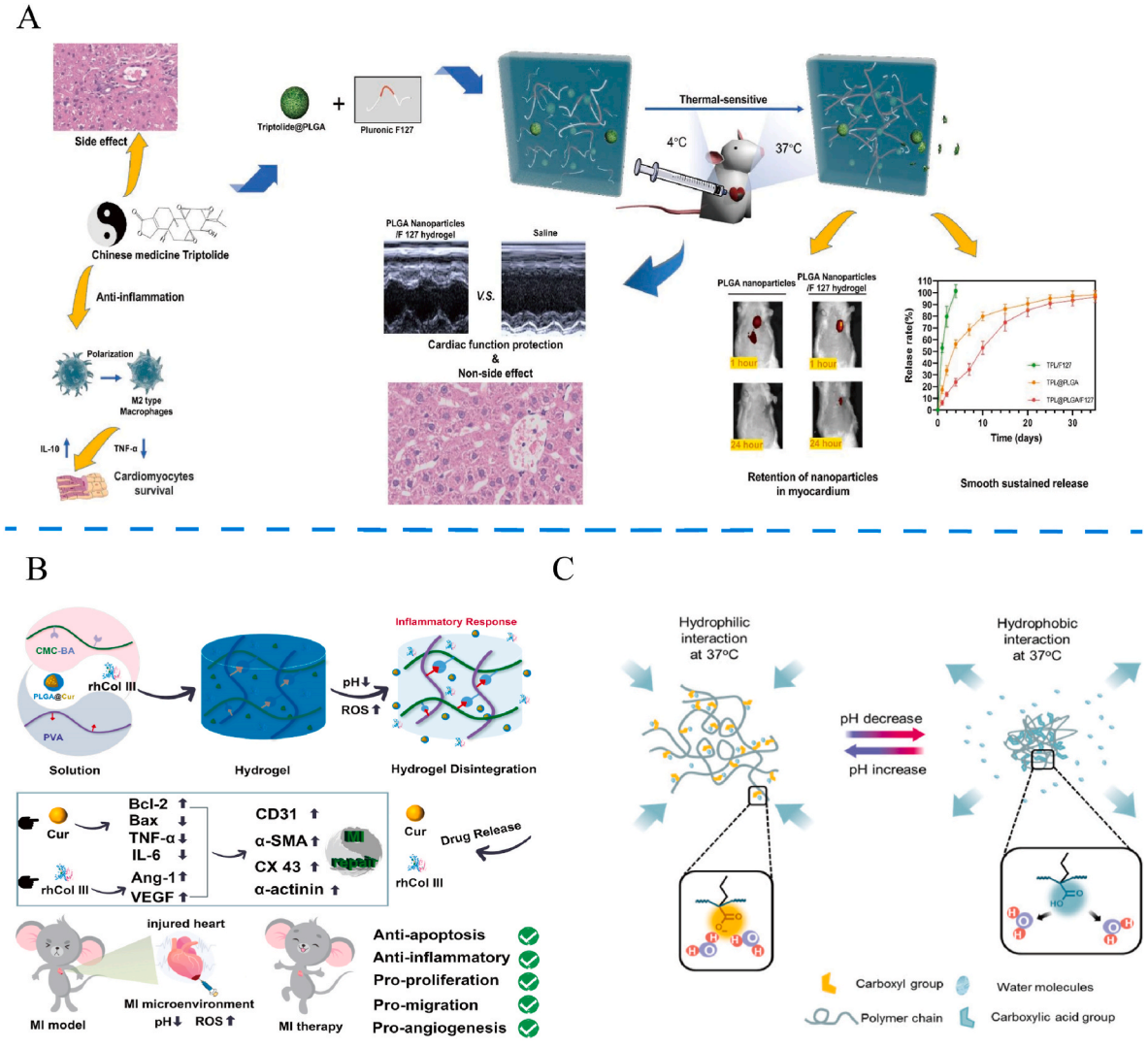

Fig. 2. A schematic diagram illustrating the application of temperature-sensitive hydrogels and pH-sensitive hydrogels during the inflammatory phase of myocardial infarction. (A). Initially, the reparative effect of TPL on myocardial infarction was investigated through network pharmacology. Subsequently, a temperature-sensitive drug release system, TPL@PLGA@F127, was designed, and the therapeutic efficacy was assessed through in vitro and in vivo experiments. Adapted by permission [37]. Copyright © 2023 BioMed Central Ltd unless otherwise stated. (B). The preparation process of a hydrogel system composed of curcumin-loaded PLGA nanoparticles and rhCol III, and its molecular mechanisms in the treatment during the inflammatory phase of myocardial infarction. Adapted by permission [41]. Copyright © 2022 Elsevier Ltd. All rights reserved. (C) Schematic representation of the mechanism of action of pH-responsive hydrogel designed based on PNIPAAm. Adapted by permission [42]. Copyright © 2016 American Chemical Society.

also enhance the healing of fibrotic scars in the infarct area. Effectively prevent heart failure. Xin Yi et al.[39]established a rat model of myocardial infarction using coronary artery ligation and injected hepatocyte growth factor (HGF) and a new DPHP hydrogel into the myocardium. The results showed that HGF combined with DPHP hydrogel has a protective effect on the heart of rats after MI, decreasing infarct size, reducing apoptosis, suppressing fibrosis, and enhancing heart function. Xia Li et al. [40] prepared a thermosensitive single-walled carbon nanotubes (SWCNTs) modified PNIPAAm hydrogel (PNIPAAm/SWCNTs). The results showed that PNIPAAm/SWCNTs hydrogel can boost stem cell activation after being implanted into the heart and improve the therapeutic effect of myocardial infarction. They studied the related properties of PNIPAAm and PNIPAAm/SWCNTs hydrogels, including solvent, temperature sensitivity, and electrical conductivity. They found that the hydrogel was temperature sensitive. Below a specific temperature, it is liquid, which is conducive to injection into the body, and when the temperature exceeds a certain temperature, the hydrogel is gel-like.

In summary, the reported temperature-sensitive hydrogel has been successfully developed into an injectable form, and is safe and non-toxic after implantation into animals, with good biocompatibility. Temperature sensitivity enables the hydrogel to be injected into the myocardium in the form of liquid, and under the action of body temperature, it rapidly forms a gel in the myocardium, which is convenient for minimally invasive administration. Using the protective effect of temperature-sensitive hydrogel on inhibiting ventricular remodeling after myocardial infarction and its excellent scaffold characteristics, the establishment of a transfer system based on temperature-sensitive hydrogel is a potential research direction for clinical prevention and treatment of myocardial infarction in the future.

4.1.2. PH responsive hydrogel

Once the body undergoes pathological conditions, the pH of the internal environment may change. The MI inflammatory response is activated, producing a large number of chemokines and inflammatory factors in the first stage. The continuous death and rupture of cardiomyocytes is accompanied by the accumulation of lactic acid, resulting in a decrease in the PH of the infarct area (PH < 6.8)[25, 43].PH-sensitive hydrogels refer to the weakly alkaline or acidic groups in the polymer structure, which are ionized according to the PH environment in vivo. It has been reported in the literature that PH-responsive hydrogels achieve liquid-sol phase transition due to the fact that most of the polymer main chain contains carboxyl groups, which are ionized in an alkaline environment and remain molecular in a weak acidic environment [44]. The application principle of pH-responsive hydrogels in myocardial infarction is primarily in two aspects, similar to that of temperature-sensitive hydrogels: on the one hand, to provide support for the infarct area, and on the other hand, because of its unique properties as a carrier, it can load various therapeutic substances. The weakly acidic or alkaline groups of the polymer structure are used to release the appropriate therapeutic substances in accordance with the local PH response, effectively prevent cardiomyocyte death, encourage their proliferation, and prevent negative outcomes such as heart failure caused by persistent inflammatory reactions.

Collagen is a natural biopolymer that maintains the natural structure within the bodies of animals. In the report by Cheng Hu et al. [41], a recombinant human type III collagen (rhCol III), structurally similar to natural collagen, undergoes a series of processes (Fig. 2B). Using the gene sequence of human collagen functional regions as a template, they retain highly cell-active fragments with minimal species and batch production differences, addressing the challenges of clinical translation. Consequently, they explore the effectiveness of rhCol III in tissue repair after MI and attempt to elucidate the underlying mechanisms. During the initial inflammatory stage of MI, the use of small-molecule anti-inflammatory drugs, such as curcumin, is crucial. Building upon this design concept, they combine the 3-aminophenylboronic acid groups of CMC-BA polymer with the dihydroxy groups of polyethylene glycol, forming boronate ester bonds to create a pH-responsive hydrogel. Subsequently, curcumin-loaded PLGA nanoparticles and rhCol III are incorporated. The results reveal that in the acidic environment post-MI, the hydrogel degrades, releasing curcumin on demand. This effectively reduces the expression levels of TNF-α and IL-6, exerting a significant inhibitory effect on cell apoptosis. Simultaneously, it efficiently promotes the expression of Ki67 and markers of vascular formation, demonstrating its capacity to enhance cell proliferation and the formation of new blood vessels. The developed hydrogel integrates various functionalities, with a straightforward preparation process, excellent biocompatibility, and responsive release of curcumin and rhCol III.

Maartje et al.[45]constructed a porcine myocardial infarction model and developed a supramolecular hydrogel with pH switchable. The hydrogel can be switched to a liquid state with PH > 8.5, at which time the viscosity is low and can pass a catheter of 1 m in length. When in contact with the tissue, it can quickly turn into a gel, providing mechanical support for the heart. The PH-responsive hydrogel significantly alleviated the inflammatory response in a pig myocardial infarction model. In addition, Li et al. [42] created a PH-and temperature-dependent dual-sensitive injectable hydrogel PH-sensitive and heat-sensitive poly (NIPAAm-co-PAA-co-MA-PEG-co-HEMA-oTMC). It is a liquid state at PH 8.0 and 37 °C, and can be injected into the infarct area through a catheter. At PH 6.5 and 37 °C, it can quickly gel into a coagulate (Fig. 2C). It effectively provides support for the early stages of myocardial infarction, facilitating the restoration of cardiac function. PH and temperature-responsive hydrogels can also be loaded oncostatin M[27]. In the rat myocardial infarction model, the biological factor can be released according to local PH, which can promote cardiac angiogenesis and cardiomyocyte proliferation, effectively inhibit myocardial fibrosis, and prevent heart failure. It is worth mentioning that the hydrogel effectively inhibits the inflammatory response of myocardial tissue after infarction.

PH hydrogels contain dissociable groups, and the formation of a gel depends on a slight change in PH in the internal environment of the body and mutual repulsion between charges, resulting in mutual entanglement between molecular chains. pH-sensitive hydrogels have proven to have good and broad application prospects for the clinical treatment of myocardial infarction. However, there remains a large gap between pH-sensitive hydrogel drug delivery systems and their clinical applications in terms of myocardial tissue targeting, precisely controlled release of therapeutic substances, and safety. This requires researchers to conduct in-depth research on the selection, design, and safety of biomaterials to provide an effective means of achieving precise delivery.

4.1.3. ROS scavenging hydrogel

One of the most metabolically active organs in the body is the heart. Therefore, myocardial cells require considerable mitochondrial energy. Mitochondria are the most important sources of reactive oxygen species (ROS). When MI occurs, myocardial cells become ischemic and hypoxic, resulting in mitochondrial dysfunction in myocardial cells, impaired ATP metabolism, and production of a large amount of ROS. Studies have demonstrated that high ROS and oxidant stress can negatively impact proteins and lipids, impede cell function, and result in cell death [46, 47]. Excess reactive oxygen species are intimately connected to early myocardial infarction inflammation. This provides a new idea for researchers to design hydrogels; that is, ROS can be used as a clinical target to encapsulate ROS scavengers in hydrogels, hoping to provide satisfactory therapeutic effects in the field of cardiovascular diseases. ROS-responsive hydrogels are mainly divided into two types according to the type of ROS scavenger: one is inorganic nanoparticles, including iron oxide nanoparticles, carbon nanoparticles, and gold nanoparticles; the other is organic groups, including phenolic and sulfur groups. The goal of most ROS-responsive hydrogels is to remove the extracellular ROS. Extracellular ROS, especially H_2O_2, which has the longest half-life, are the main targets for ROS-responsive hydrogel removal. Other ROS-scavenging drugs can also be incorporated into ROS-responsive

hydrogels. When they reach the targeted position, they are released from the hydrogel and have a synergistic therapeutic effect with the hydrogel. In light of this, it is anticipated that this ROS-scavenging hydrogel will establish itself as a novel approach for the management of MI inflammation.

An excess of ROS further induces the secretion of inflammatory factors. At this juncture, macrophages predominantly exhibit the M1 phenotype, exacerbating severe inflammation. Developing safe and effective biomaterials to facilitate ROS clearance and promote the generation of M2 macrophages for enhanced cardiac function recovery remains a significant challenge in recent years. Extracting natural small molecules from living organisms is a common approach in biomedical research. Spherical melanin nanoparticles (MNPs) with excellent dispersion are extracted from squid ink, possessing captivating biocompatibility and containing various amino acids and polysaccharides. Natural MNPs have demonstrated substantial potential in inducing phenotypic changes in macrophages and tissue repair, particularly in tumors. Hydrogels containing artificial melanin nanoparticles also exhibit outstanding antioxidant properties in tissue repair. Alginate is mostly found in the cell walls and intercellular mucilage of brown algae as well as in certain bacteria, including Pseudomonas and nitrogen-fixing bacteria, that generate sticky capsules. When alginate encounters calcium ions, a hydrogel with a three-dimensional network is formed. Jin Zhou et al. [48]constructed a natural MNPs/alginate hydrogel crosslinked with divalent cations (Ca2+) to investigate its ability to regulate oxidative stress and macrophage phenotype in the infarcted area. In vivo experiments were conducted using a rat myocardial infarction model (Fig. 3A). Encouragingly, injection of MNPs/alginate hydrogel was found to eliminate early ROS levels in the heart, preventing pathological cell death of myocardial cells. To assess the impact of MNPs/Alg hydrogel on macrophage phenotype, surface markers were examined, revealing a significant upregulation of CD206 (M2 macrophage marker) expression and a decrease in CD68 (M1 macrophage marker) expression. In summary, MNPs/Alg hydrogel, composed of natural substances from two marine sources, downregulates pro-inflammatory M1 macrophages and induces macrophage phenotypic

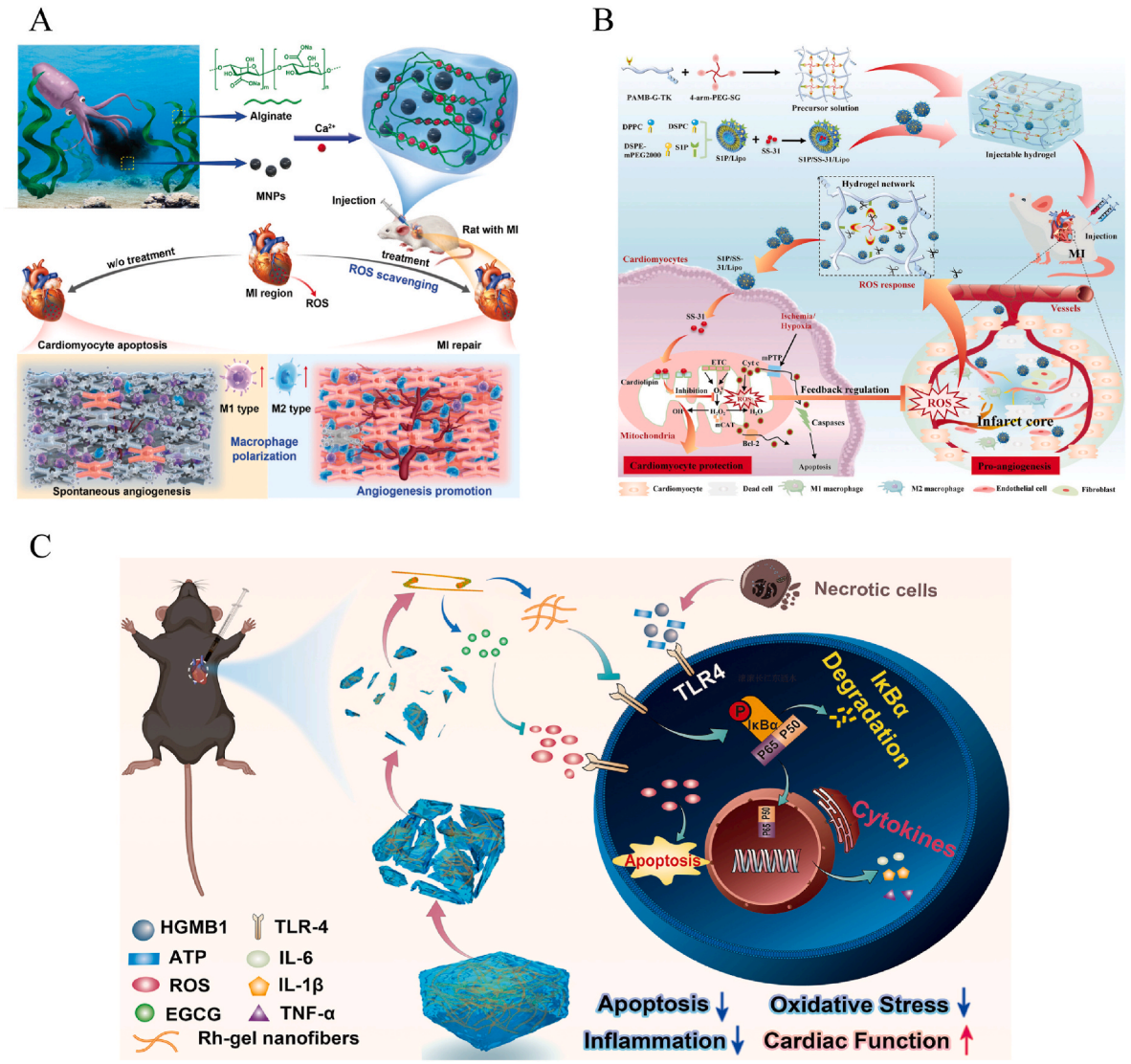

Fig. 3. Schematic illustration of a responsive hydrogel designed for clearing excessive ROS levels in the early stages of myocardial infarction. (A) The preparation process of MNPs/Alg hydrogel and its application in the molecular mechanisms during the early stages of myocardial infarction. Adapted by permission [48]. Copyright © 1999–2023 John Wiley & Sons, Inc. All rights reserved. (B) Design rationale and mechanism of action for the composite hydrogel encapsulating S1P/SS-31/Lipo. Adapted by permission [49]. Copyright © 1999–2023 John Wiley & Sons, Inc. All rights reserved.(C) Mechanistic insights into the action of EGCG@Rh-gel for ROS clearance and restoration of cardiac function. Adapted by permission [50]. Copyright © 2022 Acta Materialia Inc. Published by Elsevier Ltd. All rights reserved.

transformation to anti-inflammatory M2 type 1–3 days after treatment. Therefore, this composite hydrogel exhibits a synergistic effect in modulating the early inflammatory microenvironment of myocardial infarction and facilitating macrophage transformation, thereby alleviating the progression of MI.

After myocardial ischemia occurs, excessive ROS and inflammation are identified as the primary causes of further damage to myocardial cells. Currently, it is widely acknowledged that damaged myocardial cells release danger-associated molecular patterns (DAMPs) to activate TLR4 receptors, inducing the aggregation of immune cells. At this stage, immune cells overexpress NADPH oxidase, promoting ROS generation. In other words, there is a vicious cycle wherein the production of ROS and the composition of inflammation mutually reinforce each other. ROS and TLR4 are pivotal components in this cycle. Therefore, blocking TLR4 and attenuating ROS production represent plausible therapeutic approaches for myocardial infarction. Rhein, isolated from the crucial medicinal herb rhubarb, is a compound exhibiting anti-inflammatory activity. It has been observed that Rhein exerts its anti-inflammatory effects by inhibiting the TLR4/NF-κB signaling pathway [51]. However, the clinical application of Rhein is severely hampered by its poor water solubility and low stability. Another substance that has garnered attention for its ability to eliminate ROS is epigallocatechin gallate-3-gallate (EGCG), a polyphenolic hydroxyl aromatic molecule found in green tea. EGCG has proven effective in preventing cardiovascular diseases and cancer [52,53]. Over the past five years, scientists have been diligently working on developing hydrogel-based drug delivery systems to enhance the utilization of small-molecule drugs. Loading the anti-inflammatory Rhein and the antioxidant EGCG into injectable hydrogels as part of the same delivery system could be an effective strategy to both alleviate inflammation and inhibit ROS. The team led by Xu Liao [50] utilized Rh-gel to form π-π conjugation and hydrogen bonding with EGCG, promoting the formation of EGCG@Rh-gel (Fig. 3 C). Using C57BL/6 mice with left anterior descending coronary artery ligation for 30 min to induce MI, the researchers injected hydrogel into the infarct border zone post-MI. Results indicate that Rh-gel exhibits certain ROS-clearing properties, and the addition of EGCG further enhances this effect. Furthermore, EGCG@Rh-gel inhibits the expression of proteins related to the TLR4/NF-kB signaling pathway and inflammatory factors in the infarct area, reduces fibrosis, modulates the microenvironment of the infarct zone, effectively improves cardiac function, and achieves dual inhibition of the inflammatory pathway and oxidative stress. This successful development of a novel injectable hydrogel offers a promising therapeutic approach for treating myocardial infarction.

ECM is a complex network composed of macromolecules synthesized and secreted by various tissues and cells in the body. The ECM forms the cytoskeleton of tissues and organs, regulates tissue development, and provides the microenvironment required for cell growth. It plays an important role in maintaining the normal structure and function of the heart, and in cell growth and differentiation. Curcumin, an organic compound produced from turmeric, has been shown to have anti-inflammatory and antioxidant properties [54]. It has also been shown to minimize the buildup of collagen and aid in the recovery of heart function. Inhibiting the transformation factor (TGF-β) -SMAD2/3 signaling pathway may be a potential method [55]. Curcumin has the capacity to restore heart function, however, its application in myocardial infarction has been restricted owing to its weak water solubility and rapid metabolism inside the body, its application in myocardial infarction has been restricted [56]. As a result, curcumin has to be contained in a suitable carrier. Owing to their high biocompatibility and low immunogenicity, exosomes are thought to be able to deliver curcumin, prevent in vivo curcumin degradation, require fewer medications, and enhance treatment effectiveness. Studies have suggested that exosomes may play a role in heart repair in vivo. However, because of the heart's pumps blood and other physiological functions, exosomes injected directly into the body are removed, leading to a very low retention rate, making it impossible for them to serve a good therapeuticpurpose [57]. Exosomes may be transported by dECM hydrogels, which can function as carriers of bioactive compounds and increase the retention rate of exosomes in vivo [58]. Curcumin, exosomes, and dECM hydrogel each have specific benefits, therefore Wangyuanyuan et al. [59] combined them to create an injectable complex hydrogel. The in vivo and in vitro tests revealed that the hydrogel prevented myocardial fibrosis, increased curcumin solubility in the body, sustained the release of curcumin in the infarct area, effectively reduced the infarct are and effectively reduced the intense inflammation after infarction.

Elmipretide (SS-33) and sphingosin-1-phosphate (S1P) were loaded into a reactive oxygen species (ROS) responsive PAMB-G-TK/4-arm-PEG-SG liposome composite hydrogel created by Zhi Zheng's team [49](Fig. 3B). SS-33 is an inhibitor of mitochondrial oxidative damage, and S1P is a signal molecule that activates angiogenesis. The damaged cardiomyocytes' mitochondrial intima can be targeted by the hydrogel PAMB-G-TK/4-arm-PEG-SG for cytochrome C, inhibiting the production of excessive ROS, improving mitochondrial dysfunction, and inducing endothelial cell. Malka [60] designed a new composite hydrogel based on ECM -gold nanoparticles (AuNPs) to develop a new method for cardiac therapy. AuNPs have antioxidant properties, and are easily endocytosed by cells due to their nanoscale size. In particular, its special structure and group make it possible to simulate the biological activities of various enzymes such as superoxide dismutase and catalase, and can eliminate excessive ROS produced at the myocardial infarction site. In the hydrogel developed by the team, gold nanoparticles targeted myocardial tissue with high levels of ROS and used their own characteristics to eliminate ROS. In an ischemia-reperfusion (I/R) mouse model, the composite hydrogel showed the ability to absorb ROS, which significantly reduced ROS levels, protected the myocardial infarction area, and prevented cardiac function from deteriorating.

After MI, immune cells, especially macrophages, participate in the normal repair processes. Macrophages must transform from an inflammatory M1 phenotype to a repair-promoting M2 phenotype, which is conducive to reducing chronic inflammation and fibrosis [61,62]. Excessive ROS mainly exists in the form of H_2O_2. Ding 's team [63] used these two biological characteristics to develop a new ROS-sensitive injectable hydrogel with excellent therapeutic effects against myocardial infarction. They performed Michael addition reaction between the double bond of polyethylene glycol diacrylate (Mn = 575, PEGDA575) and the amino group of the ketone thiol diamine to form a hyperbranched polymer with a double bond end group (HBPAK). ROS can undergo redox reactions with HBPAK terminal double bonds. The hydrogel was made in 3s by polymerizing methacrylate hyaluronic acid (HA-MA) with a synthetic ROS-cleavable hyperbranched polymer under UV irradiation. Hydrogel-loaded catalase (CAT) is usually located in the cytoplasmic matrix and peroxisome, and has a heme part as an active site for the decomposition of hydrogen peroxide into water, which can effectively remove ROS. In a rat myocardial infarction model, scientists injected ROS scavenging and O_2 generation hydrogel. The results revealed that the hydrogel absorbed excessive ROS, generate O_2, inhibited apoptosis, increased the proportion of M2/M1 macrophages, promoted angiogenesis, improved heart function and reduced infarct size. Compared to traditional or CAT-free hydrogels, it shows excellent therapeutic effects on MI and significantly reduces inflammation.

Nitric oxide (NO) is crucial for safeguarding and controlling the cardiovascular system [64]. Myocardial infarction inflammation and excessive ROS levels have inhibitory effects on this cardioprotective factor. L-arginine (L-Arg), a substrate for NO formation, generates 1:1 equimolar amounts of NO and 1-citrulline through a series of complex oxygen-dependent five-electron transfer reactions in vivo [65]. L-Arg regulates NO production in the body, but its non-specific diffusion and low bioavailability result in insufficient efficacy. Therefore, multifunctional NO hydrogel delivery systems have been developed to control NO release in target tissues. Vong et al. [66] et al. designed a hydrogel with redox properties to regulate local NO levels during myocardial

infarction. Their design ideas were as follows: NO-producing enzymes and nitrate-nitrite-NO pathway are the main ways to produce NO in the body. Extracellularly, L-arginine usually produces NO when it binds to heme catalysed by endothelial nitric oxide synthase (eNOS). However, in the case of inflammation or oxidative stress in the body, eNOS uncoupling occurs, resulting in L-arginine oxidation to increase superoxide anions, rather than producing NO in the original manner. In contrast, macrophages and fibroblasts produce inducible nitric oxide synthase (iNOS). Activated macrophages increase iNOS expression, activity and NO production. However, excessive ROS in the infarct tissue blocks NO production and physiological NO signal transduction. Superoxide rapidly interacts with NO and binds to form peroxynitrite, which further damages the myocardial tissue. Therefore, based on the above ideas, the NO-RIG hydrogel designed by their team was composed of PArg-PEG-PArg and PMNT-PEG-PMNT polymers with biological functions, that could effectively control the NO level and redox balance of myocardial lesions and improve the production and bioavailability of NO. Their team used PArg-PEG-PArg coupling polyacrylic acid to increase the production of NO by regulating the activity of local enzymes in myocardial tissue. In addition, PMNT-PEG-PMNT coupled polyacrylic acid has been shown to have good redox properties in periodontitis [67], tissue anti-adhesive spray [68], and can eliminate ROS at the local injection site and maintain NO levels in the inflammatory area. In addition, the hydrogel also promoted the generation of new blood vessels in the infarction area. Although the NO-RIG hydrogel itself does not contain any drugs or bioactive factors, it has shown potential therapeutic efficiency. Therefore, this hydrogel can serve as a biological carrier and is expected to be useful for the management of cardiovascular disorders.

Excessive production of ROS is considered as one of the pathological factors that accelerates the lesions in the infarct area, and antioxidant biomaterials represented by hydrogels have been proposed to effectively treat MI. As an antioxidant, it can be introduced into hydrogels containing, inorganic metals, phenolic hydroxyl groups, and double bonds. The anti-ROS hydrogel discussed in this section showed satisfactory antioxidant activity, effectively removing excessive ROS generated after myocardial, inhibiting cardiomyocyte apoptosis, reducing inflammation and improving cardiac function. Although some progress has been made in the function of antioxidant hydrogels in cardiac tissues in recent years, there are still some problems that researchers need to work together to solve, such as mechanical properties that fail to meet clinical needs and controllable degradation rates in vivo. Although current research still faces challenges, it is believed that in the near future, with the deepening of research, ROS-responsive hydrogels will have broad application prospects and are expected to lead to a great breakthrough in the clinical treatment of myocardial infarction.

4.1.4. Conductive responsive hydrogel

Healthy heart tissues require regular electrical pulse maintenance, to allow cardiomyocytes to contract and relax. Following a myocardial infarction, an obvious or persistent inflammatory response causes rational remodeling of cardiomyopathy. Necrotic cardiomyocytes are replaced by disorganized fiber tissue, and the electrical conductivity and contractile function of the cardiomyocytes are severely compromised, which harming cardiac function. Therefore, restoring the electrical conductivity of cardiomyocytes is a potential therapeutic strategy for controlling inflammation during MI [69]. According to the literature, conductive hydrogels can promote the assembly of cardiomyocytes into a functional syncytium and restore their electrical conductivity [70]. Unfortunately, most cardiac injectable scaffolds are currently non-conductive, making it difficult to develop conductive hydrogels using tissue engineering.

By adding lignosulfonate-doped polyaniline (PAN/LS) nanorods, adeno-associated virus encoding vascular endothelial growth factor (AAV9-VEGF), and the basic skeleton of calcium-crosslinked alginate hydrogel, Wu et al. created an injectable conductive hydrogel (Alg-P-AAV hydrogel) with antioxidant, anti-inflammatory and angiogenic ability [71]. After Alg-P-AAV was implanted into rats with myocardial infarction, the ejection fraction (EF), fractional shortening (FS), and left ventricular end-diastolic diameter (LVIDd) showed obvious therapeutic effects. The findings indicated that when the Alg-P-AAV hydrogel was injected into rats with myocardial infarction, the generation of myocardial gap junctions and angiogenesis were greatly improved, the infarct area was significantly reduced, and cardiac function was restored. Research has shown that hydrogels loaded with tetraaniline (TA) nanoparticles exhibit electrical conductivity similar to normal myocardium, leading to increased expression levels of the protein CX43, which aids in promoting cardiac function recovery. Hypoxia-inducible factor-1α (HIF-1α) is a transcription factor that responds to changes in available oxygen in the cellular microenvironment, particularly in conditions of reduced oxygen or hypoxia. HIF-1α regulates the transcription of over 40 genes, including erythropoietin, glucose transporters, vascular endothelial growth factor, promoting oxygen delivery or facilitating hypoxic metabolism [72–74]. Research has found that prolyl hydroxylase (PHD) inhibitors can block post-translational hydroxylation modification of HIF-1α, stabilizing and functionally transcribing HIF-1α [75,76]. Recently, a small molecule drug, 1, 4-dihydroquinoline-4-1-3-carboxylic acid (DPCA), has been identified as an effective stabilizer of HIF-1α and an inhibitor of hydroxylases [77]. However, systemic delivery of such hydroxylase inhibitors may lead to adverse reactions, necessitating the development of new delivery systems for targeted delivery while reducing the drug dosage [78]. Moreover, DPCA's poor water solubility and short half-life have hindered its therapeutic applications. Wei et al. [79] addressed these challenges by using hyaluronic acid (HA) and ALG-CHO as a matrix, incorporating TA into ALG-CHO to confer electrical conductivity to the hydrogel (Fig. 4 A). They then prepared DPCA as nanoparticles using a reprecipitation method, coating the surface with polydopamine (PDA) to form nano-drugs (DPCA@PDA). Crosslinking ALG-CHO with DPCA@PDA resulted in the formation of a conductive hydrogel. Injecting this hydrogel into the infarcted area in a rat MI model reversed the adverse microenvironment, improved myocardial cell electrical conduction, suppressed the release of inflammatory factors, and promoted the formation of new blood vessels. In summary, they reported a conductive hydrogel based on the natural biopolymers ALG and HA, exhibiting excellent biocompatibility and rescuing cardiac function in infarcted myocardium. However, the study has certain limitations: firstly, while proposing a novel treatment strategy, the exact mechanism of action remains unclear; secondly, to validate the hydrogel's anti-inflammatory and conductive abilities, immediate injection into the infarcted area post-MI is recommended, which differs from the practical clinical application of injectable

biomaterials. In future research, the delivery time and more minimally invasive injection methods of the hydrogel should be explored; finally, the interaction between this biomaterial and relevant cardiac cells requires further investigation in future studies.

Yang Liu et al. [82] synthesized acrylic ester-modified poly (2-((2-hydroxy-3-(methacryloyloxy)propyl)dimthylammonio)acetate) (PCB-OAA) amphiphilic copolymers through thermally induced polymerization and subsequent acylation reactions. They then prepared PCB-OAA hydrogels by performing a Michael addition with dithiothreitol (DTT) (Fig. 4D). The hydrogel was injected at different locations on the backs of mice. Through experiments including ultrasound echocardiography and detection of inflammatory factors, it was discovered that PCB-OAA hydrogel exhibited excellent protective effects on myocardial infarction, significantly reducing the expression levels of TNF-α in the infarcted area. Furthermore, they found a higher vascular density in the infarcted area of the PCB-OAA group, possibly due to the hydrogel's ability to induce macrophage activation and promote the expression of vascular endothelial growth factors. Connexin 43 (CX43) plays a crucial role in cardiac electromechanical coupling. The results indicated that the hydrogel treatment group enhanced electrical signal

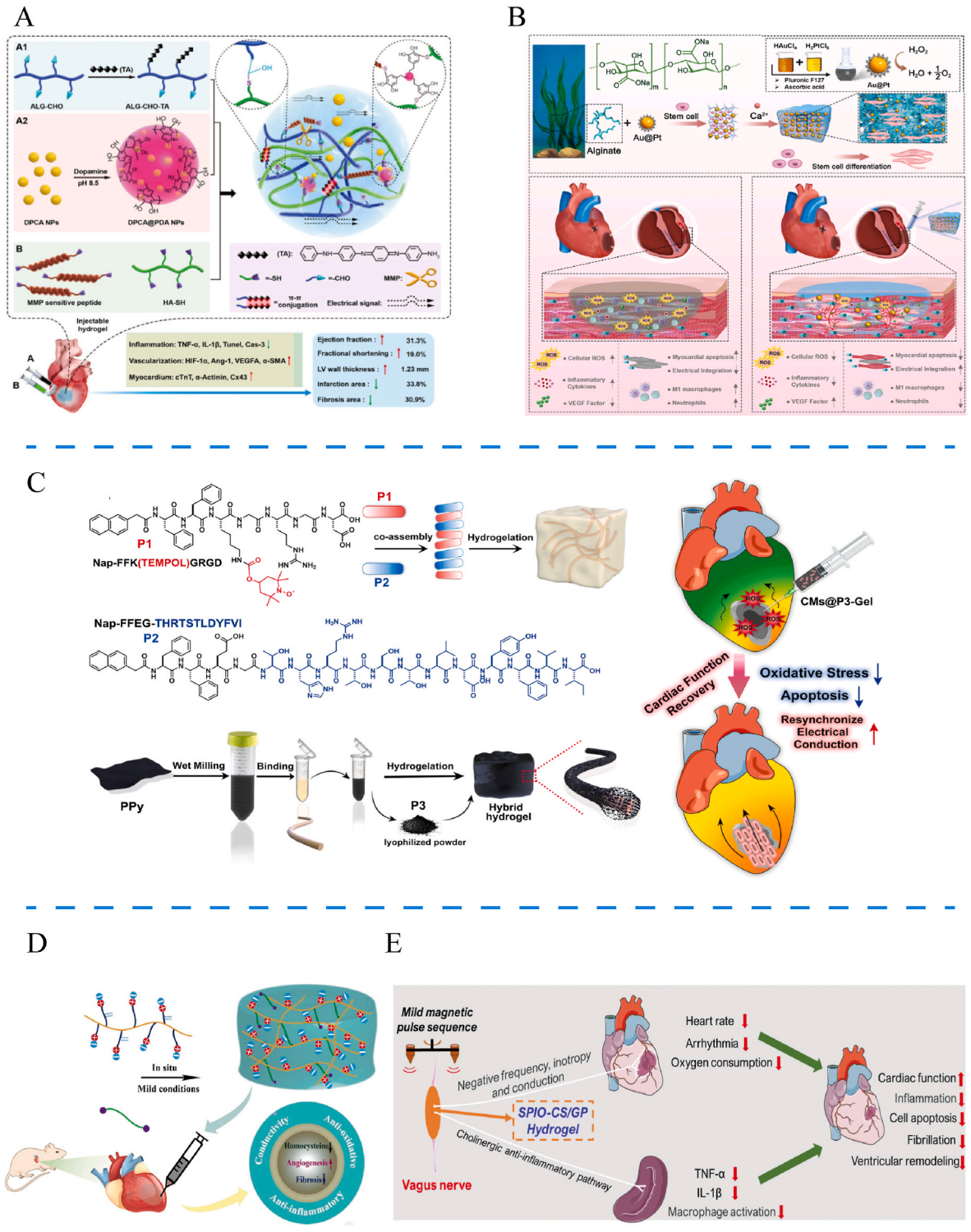

Fig. 4. (A) Design rationale for hydrogels with MMP degradation and conductivity: Utilizing functionalized hyaluronic acid (HA) and alginate (ALG), conductive tannic acid (TA) is loaded into ALG-CHO, imparting electrical conductivity to the hydrogel and creating a multifunctional system. The prepared hydrogel is then intramyocardially injected into infarcted rat hearts to assess its ability to restore early electrophysiological function in myocardial infarction. Adapted by permission [79]. Copyright ©2023 Ivyspring International Publisher.(B) Schematic representation of the preparation of Au@Pt/Alg hydrogel and its therapeutic mechanism for in vivo cardiac function restoration. Adapted by permission [80]. Copyright © 2023 The Authors. Published by American. (C) The injectable process of preparing a conductive composite hydrogel and its application in myocardial infarction repair. Adapted by permission [81]. Copyright © 2022 Elsevier Ltd. All rights reserved. (D) Schematic representation of the Mechanism of Action of PCB-OAA Hydrogel. Adapted by permission [82]. Copyright © 2021 Elsevier B.V. All rights reserved. (E) The Mechanism of Vagus Nerve Modulation in Attenuating Early Inflammatory Responses and Enhancing Cardiac Function in Myocardial Infarction. Adapted by permission [83]. Copyright © Royal Society of Chemistry 2023.

conduction, increased the expression of CX43 in vivo, and restored electrophysiological function after myocardial infarction. Importantly, the amphiphilic copolymer hydrogel's sulfur ether bonds possessed hydrolytically degradable characteristics. In conclusion, when injected into an animal model of myocardial infarction, this hydrogel effectively improved the microenvironment, restored electrical pulse signals, repaired cardiac function, and underwent degradation in vivo.

The early oxidative stress and inflammation activation in the initial stages of MI represent critical mechanisms. Rebuilding the conduction microenvironment post-infarction to promote electrical conduction is a pivotal objective in myocardial regeneration, garnering significant attention in recent years, particularly in the design of hydrogels by researchers. Gold nanoparticles (AuNPs), owing to their high conductivity and biocompatibility, have been widely applied as ideal nanomaterials for MI repair [84]; however, their application is hindered by elevated ROS levels post-infarction, which further damage cells. Platinum nanoparticles possess catalytic and antioxidant activities, but their high cost necessitates the synthesis of bimetallic nanoparticles with a high platinum surface area [85]. It has been reported that Au@Pt nanoparticles with dendritic platinum shells significantly reduce the usage of platinum, enhancing ROS clearance. Building upon these foundations, Liu et al.[80]developed injectable hydrogels with dual functionality using Au@Pt nanoparticles/calcium alginate based on early microenvironmental changes in myocardial infarction, mediated by Ca2+ cross-linking. Additionally, they loaded adipose-derived stem cells (ADSCs) onto Au@Pt/Alg hydrogels, presenting an innovative approach that combines microenvironment-modulating biomaterials with stem cell transplantation for early myocardial infarction treatment (Fig. 4B). In their study, the research team ligated the proximal left anterior descending coronary artery in SD rats, followed by rapid injection using a 28-gauge needle in the infarcted and border zones, and subsequently multi-layer closure of the chest cavity. Results demonstrated that the Au@Pt/Alg hydrogel loaded with ADSCs reduced the accumulation of CD68-positive macrophages, superoxide anions, and hydroxyl radicals in the infarcted area, alleviating inflammation and regulating the ROS microenvironment in the infarcted zone significantly. The hydrogel exhibited anti-inflammatory, antioxidant, and myocardial cell action potential recovery functions, providing a novel therapeutic strategy for early MI treatment.

Conductive biomaterials are crucial for increasing intercellular communication, coordinating electrical signal transmission, and improving electrical stimulation response cell performance. Although the conductive hydrogel can be used for cardiac repair, as a cardiac cell transporter, its application is highly anticipated. However, it cannot adapt to the excessive ROS produced after myocardial infarction to a certain extent, which has a certain impact on its function. Thus, the development of bifunctional injectable hydrogels with high conductivities and oxidation resistances is required. Zhan 's team [81] prepared a supramolecular hydrogel (R&C-Gel) in which multi-component self--assembled polypeptides were connected to conductive polymers (Fig. 4C). They integrated the ROS scavenger TEM-POL into the peptide, which has the ability to scavenge free radicals [86]. They used a wet milling system to prepare polypyridine (PPy) nanoclusters, such that PPy was uniformly dispersed on the target peptide T59 in the nanofibers [87]. It is worth mentioning that the hydrogel can not only remove excessive ROS in the microenvironment, but also maintain its electrical conductivity. Parameters such as intracellular calcium content were measured. Results from echocardiography and histology demonstrated that R&C-Gel hydrogel boosted heart repair and reconstruction of cardiac function, raised LEVF, and accelerated gap junction development (Fig. 5B). Inorganic materials, such as carbon-based nanoparticles and gold-based nanomaterials, can also be utilized as conductive materials in addition to conductive polymers like polyaniline and polypyrrole combined with hydrogels. Meng et al. [88] developed biocompatible poly (2-hydroxyethyl methacrylate) (pHEMA) as a matrix, and added self-assembled rose-shaped nanotubes (RNTs) and carbon nanofibers (CNFs) to the matrix to form a new injectable hydrogel scaffold. It improves the function of myocardial cells, providing a new approach for MI treatment.

Although the clinical treatment of myocardial infarction continues to develop, the progress in the electrophysiological function of recovering normal cardiomyocytes is relatively slow. On the one hand, cardiac tissue engineering uses natural or synthetic biomaterials to provide an extracellular matrix-like environment for cardiomyocytes and provide support for infarcted areas. On the other hand, the addition of conductive materials significantly improved cardiac electrophysiological activity and promoted synchronous contraction and relaxation, making it an ideal biomaterial for the treatment of myocardial infarction.

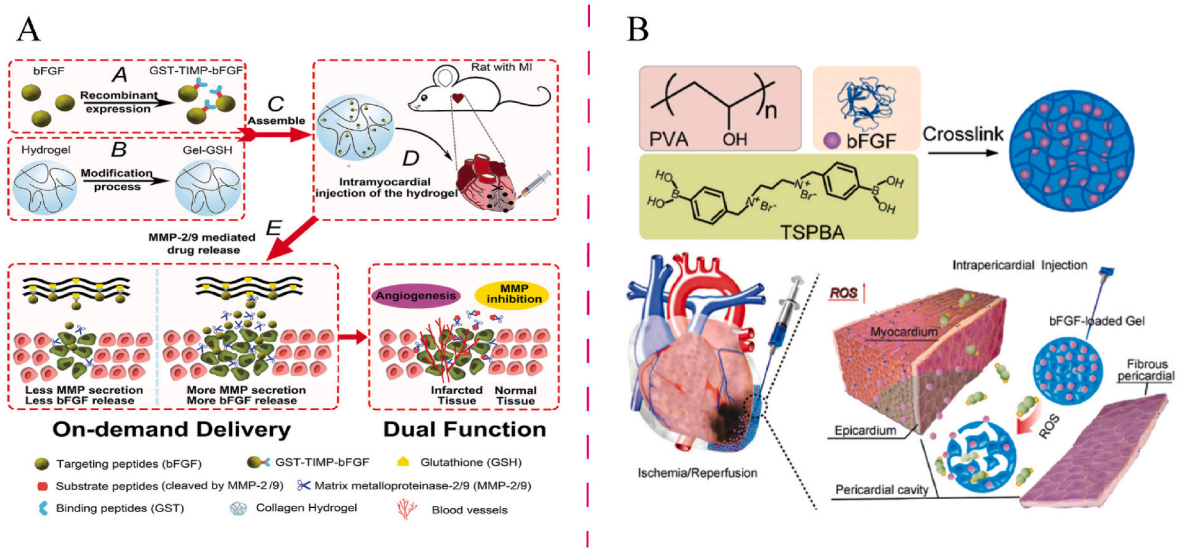

Fig. 5. Schematic diagram illustrating the therapeutic strategy of bFGF-loaded hydrogel for myocardial infarction treatment. (A) Initially, GST-TIMP-bFGF was prepared, followed by loading GSH into the hydrogel using chemical cross-linking to obtain Gel-GSH. GST-TIMP-bFGF was then mixed with Gel-GSH, forming chemical bonds through the binding of GST and GSH. The hydrogel was injected into the infarcted area to validate its therapeutic effects on myocardial infarction. Adapted by permission [134]. Copyright © 1999–2023 John Wiley & Sons, Inc. All rights reserved. (B) The preparation process of bFGF-Gel and its in vivo mechanism of action. Adapted by permission [135]. Copyright © 1999–2023 John Wiley & Sons, Inc. All rights reserved.

However, it is worth noting that the characteristics of the composite scaffold formed after the intervention of conductive materials, such as surface characteristics, structural voids, etc., must be taken into account. At the same time, the addition of conductive materials may involve electrochemical-related reactions, whether they can ensure low cytotoxicity, stability, etc., which are currently required for experimental personnel to evaluate in the synthesis of conductive hydrogels. With the continuous progress of technology and exploration, the cardiac tissue engineering application of conductive hydrogels will eventually be applied in clinical practice, benefiting patients with MI.

4.1.5. Magnetic responsive hydrogel

Dead cardiac tissue causes an inflammatory reaction and an imbalance in the autonomic nervous system after a myocardial infarction. Prompt management of the inflammatory response in the infarcted region is crucial for restoring heart function. Acetylcholine (ACh) release from the vagus nerve can be triggered by the central nervous system, according to earlier research. In order to minimize cardiac damage and inhibit inflammation, acetylcholine works on the A7-nicotinic acetylcholine receptor. This receptor then communicates with the immune system via the cholinergic anti-inflammatory pathway (CAP) [89–91]. Vagus nerve stimulation (VNS) is a fundamental application of this technique. VNS has been used in drug-resistant epilepsy and depression and has been approved by the FDA [92,93]. It has been reported that electromagnetic fields (EMFs) can affect the function and structure of cardiac autonomic nervous system (CANS) [94]. Braune et al. [95,96] found that EMFs may increase the non-thermal effect of sympathetic vasoconstrictors, promote the contraction of sympathetic vessels, inhibit atrial fibrillation, and can be used to treat arrhythmia. VNS can enhance the parasympathetic drive, restore autonomic nerve balance, and reduce systemic inflammation in patients with myocardial infarction. However, VNS requires electrode implantation, which may cause infection in vivo and other adverse reactions [93]. Therefore, it is essential to develop vagus nerve-mediated treatments.

Superparamagnetic iron oxide (SPIO) nanoparticle-loaded injectable chitosan/glycerophosphate hydrogels and gentle magnetic pulse sequences constitute an innovative magnetic vagus nerve stimulation technology created by the SiYuan Bao [83] laboratory. Injectable hydrogels with good biocompatibility can be implanted with minimal trauma using this method, which makes it possible to precisely target one vagus nerve with SPIO nanoparticles using magnetic stimulation (Fig. 4E). They first studied the characteristics and properties of the SPIO-CS/GP hydrogels and obtained SEM images of the hydrogel. The investigational team discovered that mVNS might enhance cardiac function after in situ injection of a CS/GP magnetic hydrogel into the infarcted tissue of rats. Moreover, after MI, tissue fibrosis was greatly reduced by the hydrogel, according to Masson staining. In conclusion, these findings show that the SPIO-CS/GP hydrogel, a novel magnetic hydrogel, can precisely activate the vagus nerve, limit the expression of inflammatory markers, and significantly enhance heart healing following MI.

As a traditional drug, curcumin has been confirmed by the Cox Fiona Frederike team [97] to avoid cardiomyocyte apoptosis, reduce cardiac function decline after myocardial infarction, inhibit M1 macrophage activity, and alleviate inflammation in infarcted areas. On this basis, a novel magnetic-loaded hydrogel nanocomposite was created by Mehrdad Namdari et al. [98] utilizing Fe3O4, nanogels (MNPs), and curcumin. They also constructed 10 rats heart failure using

2.5 mg/kg azithromycin. The findings revealed that in the experimental group, with the increase of curcumin nanoparticle concentration, the expression of heart failure markers decreased, and had better therapeutic effect than curcumin alone. The new magnetic stimulation hydrogel developed by the team is a magnetic stimulation generated by Fe_3O_4, which targets the drug to the infarcted area and achieves sustainable release, reducing the clinical drug dose and improving the treatment efficiency.

The electrical conductivity of myocardial tissue is conducive to the regular beating of the heart and is one of the essential conditions for maintaining normal physiological function. Hydrogels, similar to the natural ECM, have been widely used in cardiac tissue engineering. By introducing conductive materials such as inorganic nanomaterials or conductive polymers, hydrogels can be endowed with conductivity, effectively promoting cardiac function repair. Reduced graphene oxide (rGO) is typically graphene oxide pre-treated with oxidation, undergoing deoxygenation through methods such as chemical reduction, high-temperature graphitization, and electrochemical reduction, retaining its conjugated structure and exhibiting certain conductivity. In previous studies, a novel hydrogel was developed by introducing dopamine-polymerized graphene oxide (PDA) into the hydrogel. This hydrogel demonstrated excellent biocompatibility and enhanced conductivity of cardiac muscle cells in rats. Importantly, under electrical stimulation, the hydrogel exhibited a synergistic effect in promoting cardiac function recovery. Mechanical anisotropy is crucial for the heart. The pumping function of the heart is primarily caused by the contraction of anisotropic myocardial cells. In fact, most widely used hydrogels are formed by the uniform dissolution, polymerization, or assembly of molecules in hydrophilic media, exhibiting isotropic behavior. Therefore, these hydrogels do not effectively display electrophysiological anisotropy. Based on this, researchers have developed methods for preparing anisotropic hydrogels, such as electrospinning and microfluidics [101–103]. However, these techniques involve expensive and complex production procedures [104]. Therefore, there is a need to develop new methods, such as 3D printing, external electric fields, and magnetic fields [105,106]. Among these, magnetic fields can non-destructively penetrate tissues and are widely used in the preparation of anisotropic hydrogels. The combination of superparamagnetic Fe3O4 NPs and rGO has been used to form nanoparticles for electrochemical sensors [107, 108]. However, these preparation methods involve the use of toxic reducing agents and are not suitable for the preparation of hydrogel scaffolds for cell culture. It has been reported that using dopamine from shellfish reduces graphene oxide (GO), producing catechol groups that enable in situ chelation and reduction of metal ions into NPs. This process not only enhances conductivity but also imparts magnetism to the hydrogel. When the hydrogel is exposed to a magnetic field, it forms a three-dimensional anisotropic hydrogel scaffold, simulating the structural characteristics of normal myocardial tissue. In the study by Xiaopei Li et al. [109], they developed a 3D anisotropic electromagnetic hydrogel (GelMA-PDA-rGO-Fe3O4) based on the above concept, aiming to observe whether it could restore the physiological function of cardiac cells after myocardial infarction. The results indicate that the anisotropic structure of this hydrogel effectively promotes the regular contraction of myocardial cells in infarcted rats, significantly improving heart function. This study innovatively developed a new magnetic-responsive hydrogel, providing a new therapeutic approach for myocardial infarction treatment.

Traditional injectable hydrogels lack conductivity and require the addition of conductive materials such as poly-pyrrole, carbon nanotubes, etc. However, these organic and inorganic conductive materials may potentially exhibit cell toxicity and induce inflammatory responses [110]. Amphiphilic copolymers carrying carbon-based betaine (CB) have been widely applied in biomedical and engineering materials, with the ability to alleviate immune reactions [111]. Poly (methyl methacrylate) (PCB) hydrogels have been proven to induce macrophage activation, promoting the expression of vascular endothelial growth factors and anti-inflammatory cytokines [112]. It's noteworthy that amphiphilic hydrogels, compared to non-ionic hydrogels, demonstrate higher ionic conductivity, facilitating the transmission of ionic electrical signals [113,114].

Because the magnetic field has a two-way regulation of the nerve, it can not only induce the enhancement of the nervous system, but also make it long-term inhibition. So far, there are still few reports on magnetic responsive hydrogels. Therefore, it is necessary to further optimize

the precise magnetic stimulation of this new biomaterial to achieve more beneficial therapeutic effects on myocardial infarction.

5. Hydrogels for treating MI during the proliferative phase

ECM deposited too heavily in the myocardial infarction location will turn into non-contractible fibrotic scars in the second stage of MI, leading to tissue sclerosis and cardiac systolic and diastolic dysfunction. Myocardial fibrosis is a TGF-β receptor (TGF-β pathway) that binds to the cardiac fibroblast cell membrane through TGF-β in the body. Inhibition of cardiac fibrosis mediated by TGF-β pathway provides a new idea for the treatment of MI. Most of the current treatments are to inject TGFβ inhibitors or anti-TGF-β antibodies into the body [115,116]. Currently, many treatments involve injecting TGF-β inhibitors or anti--TGF-β antibodies into the body. However, these methods can only reduce myocardial fibrosis rather than addressing it at its root cause, and TGF-β inhibitors are associated with high toxicity to the body [117,118].

Biological factor studies have increasingly concentrated on enhancing vascularization in infarcted tissue and reducing cardiac fibrosis. These factors predominantly originate from cardiac stem cells. Stem cells have shown promise in enhancing cardiac function following injury. Current consensus holds that there are no native cardiac stem cells capable of direct differentiation into new cardiomyocytes for clinically significant myocardial regeneration [119]. Nevertheless, even in the absence of direct cardiomyocyte regeneration, cardiac stem cells can play a vital role by releasing specific active cytokines. Their actions include promoting neovascularization in the infarcted region, regulating post-injury inflammation, enhancing cardiomyocyte survival, and diminishing the formation of fibrotic scars. Cardiac stem cells (CSCs) are briefly introduced to repair myocardial infarction through paracrine mechanism. Its role is mainly reflected in the following three aspects [120]: (1) Improve cardiac remodeling: CSCs secrete molecules related to extracellular matrix synthesis through paracrine, effectively inhibit myocardial fibrosis, reduce the proliferation of cardiac fibroblasts, and inhibit the overexpression of collagen, thereby improving cardiac function; (2) Secretion of pro-angiogenic factors: Studies have found that inhibiting the secretion of vascular endothelial growth factor by transplanted myocardial stem cells will significantly weaken its effect on repairing myocardial infarction area; (3) Anti-apoptotic effect: This is also the most important, insulin growth factor-1 secreted by CSCs can significantly reduce cell necrosis and apoptosis in the hypoxic environment of MI.

Therefore, the use of therapeutic bioactive factors to induce the related physiological processes in the infarction area is an effective means to treat myocardial infarction. Regrettably, bioactive factors usually suffer from drawbacks such as short half-life, high diffusion rate, and low activity in the harsh environment of ischemia and hypoxia. Consequently, the long-term therapeutic efficacy of these active factors tends to be suboptimal, necessitating high single doses. This not only amplifies potential side effects but also escalates treatment costs.

5.1. Growth factor-loaded hydrogel

Thanks to the three-dimensional network structure of the hydrogel, bioactive molecules are mixed with liquid hydrogel solution and injected into the infarction area, which is combined by chemical cross-linking and physical cross-linking, and slowly released with the degradation of the hydrogel, extending the action time of the cytokines, protecting the cytokines from the degradation of proteolytic enzymes, maintaining their biological activity and improving the curative effect. At the same time, by adjusting the release rate of growth factors, their biological activity can be sustained over an extended period while maintaining an effective concentration, which not only avoids the loss of local cytokines but also avoids the side effects caused by excessive local concentration. Recent research has yielded promising outcomes, where hydrogel-loaded bioactive factors have been employed to develop tissue-engineered myocardial tissue for the treatment of myocardial infarction. Next, in this section, we will focus on the recent progress of three important bio-factor-supported hydrogels in the treatment of myocardial infarction.

5.1.1. Basic fibroblast growth factor loaded hydrogel

The family of fibroblast growth factor proteins includes the basic fibroblast growth factor (bFGF). bFGF is a trace active substance in mammals and humans, but is considered to be one of the most effective angiogenic factors. It improves heart function after MI by increasing myocardial blood flow, decreasing apoptosis, and doing so [121,122]. Unfortunately, there are few studies on therapeutic drugs for bFGF at this stage, and bFGF is easily degraded by proteins in the body, resulting in low drug build-up in the MI, causing serious side effects [123,124]. Therefore, a safe and efficient delivery strategy must be developed to increase the local bFGF concentration and reduce its adverse effects.

By using pyridyl disulfide-modified carboxymethyl chitosan (CMCS-S-S-Py) and reduced BSA (rBSA), Bo Fu et al. [125] created an injectable disulfide-crosslinked chitosan hydrogel that was loaded with bFGF in 2022. The therapeutic effects were investigated in a rat MI model. After 28 days of treatment, the heart tissues of the mice in each experimental group were obtained, and the cardiac function of the mice was evaluated by ultrasonic electrocardiography. The density of new blood vessels and the concentration of bFGF in the cardiac spine increased, promoting the proliferation and migration of mature vascular endothelial cells around the site of myocardial infarction. In the extracellular matrix of healthy myocardium, type I collagen accounts for 80 %–85 % [126,127]. Many collagen-based hydrogels have been reported to improve cardiac repair following MI [128–130]. The presence of type I collagen in the infarcted area during wound healing after myocardial infarction is not a bad thing in itself. However, excessive cross-linking after type I collagen deposition promotes scarring and irreversible ventricular remodeling in the infarcted area. It can be seen that the modification of the deposited type I collagen and its extensive cross-linking into a rigid scar in the infarct area are fatal for patients. Type I and III collagen appear to undergo uneven deposition as MI fibrosis progresses [131]. Li ‘s team [132] used this biological feature to load basic fibroblast growth factor into a gelatin hydrogel (bFGF-GHS hydrogel) to change the collagen subtype, thereby improving the left ventricular function in rats with chronic MI. After 4 weeks of myocardial infarction induction, the bFGF-GHS hydrogel was placed directly in the myocardial infarction area of the rats by thoracotomy. After four weeks of treatment, immunohistochemistry and qPCR analyse were performed. The results showed that bFGF-GHS hydrogel induced neovascularization, improve cardiac function, and reduce ventricular dilatation and remodeling. It is important to note the ability of the hydrogel to reduce type I collagen expression while increasing the proportion of type III collagen.

bFGF, as a growth factor, its sustained release can alleviate ECM degradation and adverse proliferation after myocardial infarction. Matrix metalloproteinases (MMPs) are members of the zinc endopeptidase family, and their expression levels are significantly increased in cancer and heart disease. The overexpression of MMPs has been associated with the severity of myocardial infarction [133], thus, the excessive activation of MMPs may serve as a target molecule for drug release. Therefore, it is necessary to develop a system that can respond to the expression levels of MMPs after myocardial infarction, in order to deliver bFGF as needed, target the infarcted area, and effectively alleviate adverse ventricular remodeling after myocardial infarction. Fan and colleagues [134] used

glutathione (GSH)-modified collagen hydrogel (Gel-GSH) to prepare recombinant protein GST-TIMP-bFGF. This recombinant protein consists of bFGF, glutathione S-transferase (GST), and MMP-2/9 cleavable peptide PLGLAG. The team’s design approach is as follows: the specific binding of GST and GSH enhances the loading capacity of the hydrogel for the recombinant protein, and the cleavable peptide responds to the concentration of overexpressed MMP-2/9 in the infarct area, achieving

on-demand release of bFGF (Fig. 5A). Through a series of experiments, it was found that after 8 days of treatment, the amount of released bFGF in the GST-TIMP-bFGF group increased significantly compared to the other experimental groups, and it was consistent with the upward trend of MMP-2/9 after myocardial infarction, indicating that the hydrogel can release bFGF specifically in response to MMP-2/9 overexpression to a certain extent. They studied the therapeutic effect of Gel-GSH on a rat model of myocardial infarction and found that the group treated with GST-TIMP-bFGF-loaded hydrogel showed the most significant effect in alleviating adverse myocardial proliferating. Additionally, after injecting this hydrogel into normal mice for one month, no serious immune reactions were observed. Furthermore, due to the angiogenic effect of bFGF, the group with GST-TIMP-bFGF-loaded hydrogel showed increased new blood vessel density in the infarct area, improving heart function. Therefore, responsive release of bFGF may become a promising therapeutic strategy for myocardial infarction during the proliferative phase.

Another responsive release hydrogel for bFGF has been developed. Currently, there are four main routes of administration for hydrogels, including intramyocardial injection, intracoronary injection, intravenous injection, and cardiac patch, but all have certain limitations, thus necessitating the development of new delivery methods. The pericardium is a membranous sac covering the surface of the heart, consisting of fibrous and serous layers, with the space between these layers known as the pericardial cavity. Direct injection of stem cells and growth factors into the pericardial cavity has been used for cardiac tissue function [136, 137]. Intrapericardial injection (iPC) requires a carrier to effectively retain the loaded drug in the pericardial space and achieve sustained and stable drug release. After myocardial infarction, the concentration of reactive oxygen species (ROS) rapidly increases, potentially serving as a trigger for drug release. Polyvinyl alcohol (PVA) is a basic component of FDA-approved hydrogels, possessing good biocompatibility and degradability. In light of all these design concepts, Zhenhua Li et al. [135] designed a novel responsive hydrogel by combining bFGF with a ROS-responsive hydrogel (Gel-bFGF), and injected this combination into the pericardial cavity to observe whether it could serve as a therapeutic strategy for cardiac function repair after myocardial infarction. Following myocardial infarction, ROS levels remain elevated for several days, during which bFGF is continuously released into the pericardial cavity (Fig. 5B). They subsequently validated this hydrogel in rat and pig models, demonstrating that it increased the retention of bFGF in the pericardial cavity, significantly promoted myocardial cell proliferation and angiogenesis, inhibited adverse myocardial proliferating, and effectively restored cardiac function. However, this study has certain limitations, such as the need to select a hydrogel with suitable swelling characteristics for pericardial injection, as highly swelling hydrogels can lead to pericardial effusion. Additionally, further assessment of the safety and efficacy of the hydrogel is required. Haibing Wang et al. [138] combined chitosan with bFGF. After 4 weeks of injection, it was observed that the left ventricular ejection fraction and left ventricular shortening were improved, the density of neovascularization in the infarct area was increased, and the infarct area and fibrosis area were significantly reduced. In other words, the temperature-responsive chitosan hydrogel developed by the team was combined with bFGF to enhance the role of bFGF in promoting neovascularization. It plays an important role in cardiac function repair, and is a new method for infarct area repair.

bFGF has a short half-life and direct administration usually requires high doses, which can cause serious side effects. Dex-PCL-HEMA/PNIPAAm, as a temperature-sensitive hydrogel, has certain biocompatibility and degradability. Hongling Zhu's team [139] loaded bFGF into the thermosensitive hydrogel to study whether the implantation of bFGF and thermosensitive hydrogel could inhibit the adverse growth and remodeling of the infarction area and induce the formation of new blood vessels. Using a rat model of myocardial infarction, they injected hydrogel and found that bFGF supported Dex-PCL-HEMA/PNIPAAm hydrogel promoted angiogenesis, reduced infarct size and protected the heart.

Combining basic fibroblast growth factors with hydrogels improves the physiological function of fibroblasts, slows cytokine clearance in the body and maintains a relatively stable concentration in situ. bFGF levels have been shown to repair cardiac function after myocardial infarction and reduce cardiac remodeling. The combination of BFBG and hydrogels is a promising therapeutic strategy for myocardial infarction.

5.1.2. *Vascular endothelial growth factor loaded hydrogel*

Vascular endothelial growth factor (VEGF) is a member of platelet-derived growth factor family. VEGF can promote angiogenesis, increase vascular permeability, and is critical for angiogenesis [140]. In the second step of MI treatment, VEGF promotes the proliferation of endothelial cells in the infarct area, thereby promoting neovascularization [141]. New blood vessel growth is crucial for developing collateral circulation, reducing myocardial cell necrosis, and increasing blood flow [142]. Numerous studies have demonstrated the critical function of medications linked to angiogenesis in reducing the ischemia and the hypoxic milieu of myocardial infarction and limiting the continued growth of the infarct size [143–145]. However, VEGF is easily degraded in the body, has a relatively short half-life, and is rapidly lost from its target position. Therefore, long-term systemic injections of VEGF do not yield good clinical results [146]. Additionally, it has been observed that systemic VEGF injection may result in off-target angiogenesis at off-target areas, causing major adverse responses, making a person more susceptible to vascular leakage, hypotension, and tumor development [147]. Therefore, a treatment strategy to achieve controllable and sustainable release of VEGF is an urgency needed to establish a functional vascular system and improve cardiac function in MI.

Liu et al. [148] combined the biochemical advantages of alginate, stem cells and VEGF to develop injectable hydrogels that could improve the comprehensive efficacy of myocardial infarction as carriers of neonatal CMs and VEGF. They also introduced fibrin, designed to enhance cell adhesion, and VEGF as a core growth factor, the purpose of which was to promote angiogenesis in the infarct area. On the seventh days and twenty-eighth days following the injection of the Alg/Fib hydrogel into the infarcted region of the mice, echocardiography was performed to track heart function. The results showed that blood vessel density in the infarcted area increased, the infarct area decreased, the ischemic and hypoxic microenvironments significantly improved and effectively inhibit the pathological process of fibrosis during the second stage of MI.

The mesh size of the injectable hydrogels is important for capturing objects. For example, when the mesh size is in the order of tens of nanometers, it can capture VEGF and angiopoietin-1 (ANG-1) [149]. The Abdul Jalil Rufaihah team [150] loaded VEGF and ANG-1 onto polyethylene glycol-fibrinogen (PF) hydrogels. In their experiments, the new PF hydrogel can achieve an ' on-demand ' release of growth factors at the injection site, and it has been proved that the capture of growth factors by PF hydrogels does not destroy their physiological functions. By providing mechanical support to the myocardial infarction region of the rat model, the PF hydrogel reduced the severity of fibrosis proliferating there. After four weeks of treatment with MI, the amount of neovascularization increased as a result, according to the findings. The use of PF hydrogels in myocardial infarction models has been successfully demonstrated to be able to continuously and controlled release growth factors in ischemic myocardium for 30 days. It is worth mentioning that PF hydrogel dual delivery of growth factors shows greater benefits than PF hydrogel treatment alone.

VEGF specifically stimulates endothelial cell proliferation in vitro and has been considered to be effective in inducing neovascularization. VEGF has been used several times in animal and clinical trials with promising results [151]. Chitosan, as a natural hydrogel, was prepared as nanoparticle, which has the effect of drug slow release, prolonging

action time and reducing drug toxicity. Because of its unique advantages and good biocompatibility, chitosan nanoparticles have become a research hotspot. Dae-Weung Kim et al. [152] adopted this research idea and used nuclear imaging technology to track VEGF and monitor whether VEGF plays a role in angiogenesis to a certain extent, thereby promoting cardiac functional repair after myocardial infarction. Myocardial infarction model was constructed by ligation of the left coronary artery in rats, and then VEGF supported chitosan hydrogel was injected into the infarction area. The study showed that the delivery of VEGF chitosan particles resulted in a suitable concentration of VEGF retention in the heart muscle. Most importantly, there is a significant increase in neovascularization density in the myocardial infarction area, effectively inhibiting myocardial remodeling and fibrosis, which may be a powerful delivery system for improving cardiac function after myocardial infarction.

Vascular endothelial growth factor has attracted considerable interest in tissue regeneration. As an effective angiogenic signal transduction molecule, it promotes the generation of new blood vessels in the area of MI and produces satisfactory results. However, it is worth noting that both off-target effects and inadequate administration are likely to increase the risk of adverse reactions. Therefore, VEGF-loaded hydrogels require further improvement. Researchers have jointly overcome the current challenges of drug administration and provide a promising therapeutic strategy for the treatment of pathological fibrosis caused by myocardial infarction.

5.1.3. Insulin-like growth factor-1 loaded hydrogel

Insulin-like growth factor 1 (IGF-1) is a multifunctional cell proliferation regulator found in various organs and is crucial for cell proliferation, differentiation, and individual development. According to previous studies, stimulating eCSCs in the region of myocardial infarction using in situ injections of various growth factors, for example insulin-like growth factor-1, can considerably enhance heart function [153,154]. Based on its biological characteristics of IGF-1, some researchers have combined it with biomaterials to develop novel delivery systems. Li et al. [155] synthesized thermosensitive hydrogels with protein reactivity, and coupled IGF-1 and cardiosphere-derived cells to the hydrogels. Simulating the harsh environment of MI, the hydrogel was directly injected into the infarct area, indicating that the solidified IGF-1 hydrogel enhanced cell activity and maintained cell viability, and increased the change of survival and differentiation of the infarcted cardiac cells.

IGF-1 is widely known to play a crucial role in healing damaged tissues. Matsushita 's team [156] reportedly designed a thermosensitive and biodegradable hydrogel loaded with IGF-1. The hydrogel was injected immediately into the region surrounding the infarction after male rats were subjected to myocardial infarction. The results of the treatment after one week showed that the degree of apoptosis was weakened and pathological fibrosis was reduced. In a rat myocardial infarction model, the implanted hydrogel can therefore improve the restoration of heart function.

Research suggests a negative correlation between circulating levels of IGF-1 in the body's circulatory system and the risk of cardiovascular diseases [157,158]. Due to insufficient endogenous levels, exogenous injection of IGF-1 is required. However, direct injection of naked IGF-1 faces limitations in myocardial uptake, necessitating the development of new drug delivery systems. Currently, injectable alginate hydrogel has been used in Phase I and Phase II clinical trials, with its efficacy and safety confirmed [159]. After injection into the infarcted myocardial area, alginate solution can crosslink with Ca2+, thereby improving the microenvironment of the infarcted area and promoting blood vessel formation. Additionally, its biological properties are similar to the extracellular matrix (ECM) and can provide mechanical support to the infarcted area. Microsphere technology involves embedding drugs in nanoscale particle formulations of high molecular carrier materials, extending the duration of drug action, reducing dosing frequency, and minimizing toxic side effects. Silk fibroin protein (SF) is a naturally derived large molecule extracted from silkworm silk, known for its excellent biocompatibility and ease of modification. Jianguo Feng et al. [160] used a microfluidic device to prepare SF microspheres, followed by adsorption of IGF-1 onto SF microspheres. Finally, this composite was encapsulated in injectable hydrogel. The therapeutic effects of this hydrogel on myocardial infarction were studied through in vivo and in vitro experiments. They employed a rat myocardial infarction model, directly injecting the hydrogel into the infarcted area, and sacrificing the rats 7 and 28 days post-surgery to obtain corresponding tissues. The results indicated that rats in the IGF-1 hydrogel group showed significantly reduced wall thickness and fibrosis, with the smallest infarct area and reversal of pathological remodeling of the left ventricle. Importantly, compared to traditional hydrogels without SF microspheres, the release of IGF-1 in hydrogels containing SF microspheres was relatively slow, providing strong evidence for the potent utilization of biomaterials in treating myocardial infarction.

Myocardial infarction and heart failure are increasingly treated with bio-factor loaded hydrogels. Insulin-like growth factor-1 embedded in hydrogels inhibits infarct growth, and scar fibrosis, promotes angiogenesis at the infarct site, and decreases cardiomyocyte death. However, compared to the vascular endothelial growth factor and basic fibroblast growth factor introduced above, there are few reports on IGF-1, and its potential advantages and disadvantages need to be explored.

6. Hydrogels for treating MI during the remodeling phase

As MI occurs, a large number of heart muscle cells die. In the final remodeling stage, scars rich in over-crosslinked collagen eventually replace dead cardiomyocytes, further affecting normal myocardial function. Adult cardiomyocytes are terminally differentiated cells with limited proliferation capacity, rendering them incapable of effectively regenerating myocardial tissue through proliferation. The introduction of exogenous stem cells offers a potential avenue for reconstructing functional heart muscle. However, the reconstruction of necrotic myocardium is still impossible due to the excessive retention rate of transplanted cells caused by ECM degradation and myocardial compression, and the apoptosis of stem cells caused by the harsh local microenvironment of infarction. As ECM analogs, hydrogels serve as a three-dimensional growth environment for cells in vitro and mimic the properties of the ECM in vivo. The hydrogel changes from liquid phase to solid phase quickly after injection, so it can wrap the transplanted cells and improve the local retention rate of the cells, which is a very promising method for the third stage of myocardial infarction at present, and has become a research hotspot.

In recent years, RNA therapy has emerged as a promising avenue in the research of myocardial tissue regeneration and repair. It has been discovered that specific functional miRNAs can stimulate cardiomyocyte proliferation, inhibit cell apoptosis, and facilitate the formation of new blood vessels in the infarcted area. However, there are two major bottlenecks in the application of miRNA therapy in myocardial infarction. First, conventional carrier RNA delivery efficiency is low, and naked RNA is easily degraded by RNA enzymes in the natural environment and in vivo, with a short half-life. Second, RNA delivery in the heart injury area has poor efficacy, and miRNA cannot be delivered to target cells through appropriate cytocytosis pathways to achieve an effective therapeutic concentration locally. These difficulties significantly limited its clinical translational potential. Due to the characteristics of hydrogels, the researchers combined miRNA with hydrogels and found that the miRNA loading capacity, stability and transfection efficiency were improved, while avoiding degradation by RNA enzymes in vivo, which is holds the promise of offering novel therapeutic strategies for the treatment of the remodeling stage of myocardial infarction. To sum up, in this section, we focused on stem cell supported hydrogels and miRNA supported hydrogels for the treatment of the remodeling stage of myocardial infarction.

6.1. Stem cell-loaded hydrogel

There are about 2–4 billion cardiomyocytes in the human left ventricle. When myocardial infarction occurs, more than 25% of cardiomyocytes will be lost within 1 h, which is very harmful to the heart [161]. For the final remodeling stage of MI, heart transplantation presents challenges such as limited donor availability and high costs. As a result, stem cell therapy has emerged as a potential approach for treating MI, gaining favor among patients. External stem cell infusion is done to boost the directional differentiation of cells into heart cells and boost the density of cells at the infarct location [162–164].

Two elements of the stem cell-loaded hydrogel's cardiac healing process are outlined (Fig. 6). Myocardial infarction results in a significant number of myocardial cell necrosis and ECM degradation, leading to a thinning of the myocardial wall. Injectable hydrogel can exert its own advantages and provide a suitable microenvironment for the survival of infarcted myocardial stem cells. Furthermore, stem cells generate active exosomes within the infarcted region, which serve to prevent further cardiomyocyte loss and encourage angiogenesis and immune control [165,166].

Unfortunately, clinical studies have shown that stem cells or other growth factors have poor retention at the infarct site due to the poor microenvironment of ischemia and hypoxia in myocardial infarction and the strong mechanical flushing force of pulsating myocardium [167,168]. Stem cell-loaded hydrogel This is a very promising treatment for advancing current cardiac stem cell therapy. We will concentrate on the various stem cell-loaded hydrogel kinds' strategies for therapy in this section.

6.1.1. Mesenchymal stem cells loaded hydrogel

Stromal cells, known as mesenchymal stem cells (MSCs), can be extracted from a variety of tissues, including bone marrow and umbilical cord. MSCs can repair injured tissues through a variety of processes, including self-renewal and differentiation, prevent the growth of tissue fibrosis, promote the formation of fibrotic scars, and have good anti-fibrotic properties [169,170]. Some researchers believe that MSCs can differentiate into cardiomyocytes and play a role in repairing cardiac function. However, MSCs have been shown to have only some cardiomyocyte-like characteristics, but cannot differentiate into fully mature functional cardiomyocytes. Moreover, the microenvironment of the infarcted area is poor, and transplanted stem cells have difficulty surviving. Therefore, MSCs secrete growth factors and, cytokines, in the form of extracellular vesicles, and act on neighboring cells to promote angiogenesis and, anti-myocardial cell apoptosis, improve the microenvironment, and promote damage repair.

Mesenchymal stem cells (MSCs) are considered highly promising for promoting the regeneration of infarcted myocardium, releasing immunomodulatory cytokines through paracrine effects. However, stem cell therapy is susceptible to the adverse microenvironment post-infarction, such as high shear stress and elevated levels of ROS. Research has shown that when naked MSCs are injected into infarcted tissue 24 h post-infarction, only around 1% of the mesenchymal stem cells survive. By the fourth day after transplantation, the cell survival rate drops to less than 0.44% [171,172]. To enhance the survival rate of implanted stem cells, encapsulating them in hydrogels not only shields the transplanted cells from host immune reactions but also protects them from high shear stress, providing a favorable environment for cell survival. As described earlier, elevated oxidative stress levels are indicative of pathological myocardial infarction. Delivering antioxidants to the infarcted area is not feasible, necessitating the development of new materials or treatment strategies to provide antioxidant activity for transplanted mesenchymal stem cells. Graphene oxide exhibits excellent antioxidant activity and biocompatibility [173,174]. Building on this concept, Goeun Choe et al. [175] encapsulated mesenchymal stem cells in graphene oxide/alginate hydrogel. In in vitro and in vivo studies, they confirmed that this hydrogel not only reduces oxidative stress levels post-myocardial infarction but also enhances the survival rate of transplanted MSCs, effectively improving cardiac function after myocardial infarction.

An increasing body of evidence suggests that natural hydrogels such

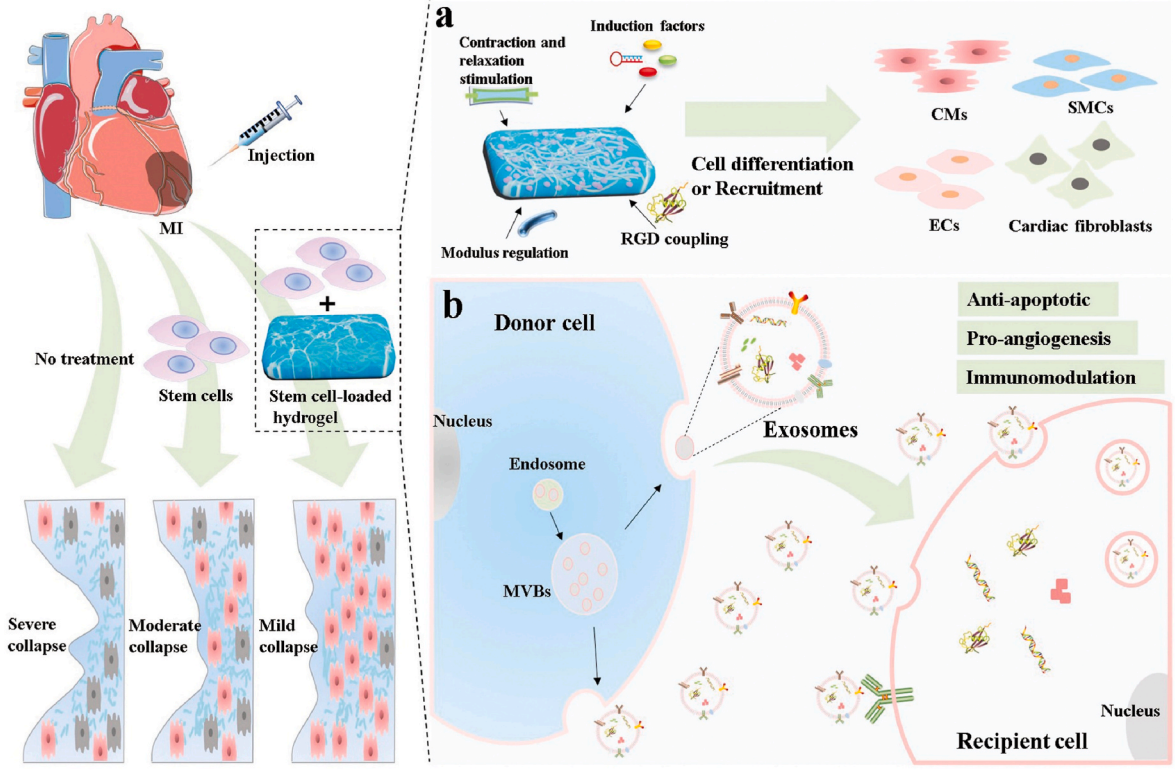

Fig. 6. A schematic diagram of the mechanism of stem cell-loaded injectable hydrogel on MI. Adapted by permission [14]. Copyright © 2021.ELSVIER B.V.

as collagen, chitosan, and alginate can enhance the survival rate of transplanted stem cells in the infarcted area, thereby improving therapeutic outcomes. A recent study revealed a significantly increased retention rate of mesenchymal stem cells with a collagen coating in the infarcted zone [176]. However, the mechanical properties and stability of natural collagen are relatively poor, posing significant obstacles to clinical applications. Therefore, optimization of hydrogels is necessary. Currently, transglutaminase has been added to collagen hydrogels (Col-Tgel). Previous research indicates that Col-Tgel exhibits superior adaptability and mechanical properties compared to collagen hydrogels, providing an optimal environment for adipose-derived stem cells (ADSCs) [177]. However, the effectiveness of Col-Tgel in the treatment of myocardial infarction has not been reported to date. Adipose-derived mesenchymal stem cells (ADSCs) are a type of stem cell with diverse differentiation potential, derived from adipose tissue. They have the ability to produce various beneficial bioactive factors through paracrine effects. In a study by Chen et al. [178], the combination of Col-Tgel and ADSCs was investigated to determine whether it could enhance the retention of transplanted cells in the myocardium and improve cardiac function. Through a series of in vivo and in vitro experiments, they found that Col-Tgel hydrogel enabled the survival and growth of ADSCs in the infarcted area for up to four weeks. This effectively suppressed myocardial cell apoptosis and fibrosis, providing better protection for cardiac remodeling after myocardial infarction. The Yuta Yoshizaki team [179] reported a biodegradable injectable hydrogel formed by temperature-responsive covalent cross-linking. The hydrogel was composed of poly (ε-caprolactone-co-ethylene glycol ester) (PCGA) and polyethylene glycol (PEG) as units to form an ABA-type triblock copolymer PCGA-b-PEG-b-PCGA. The team combined the advantages of temperature-sensitive hydrogel and AdSCs to develop a new in vivo cell delivery system. By loading AdSCs on PCGA-b-PEG-b-PCGA hydrogel and injecting it into a mouse myocardial infarction model, the therapeutic effect was observed. The results showed that the combination of AdSCs and hydrogel prolonged the retention time of stem cells at the injection site and provided support for the damaged area of myocardium. Moreover, AdSCs effectively inhibit myocardial remodeling after myocardial infarction, promote the formation of new capillaries in ischemic areas, and restore cardiac function. The use of ADSCs offers several advantages. Firstly, the acquisition of ADSCs is relatively straightforward and can be obtained through surgical procedures from subcutaneous adipose tissue, resulting in lower costs. Secondly, compared to bone marrow-derived mesenchymal stem cells, adipose tissue produces a significantly greater quantity of ADSCs, exceeding bone marrow by more than fivefold, which is a crucial factor.

Enhancing the survival rate of implanted stem cells is crucial for developing new MI treatment strategies. The implantation of stem cells requires a scaffold, and hydrogels serve as excellent choices. Chitosan hydrogel, as a type of natural hydrogel, can protect stem cells from host clearance. As previously discussed, IGF-1 is a bioactive factor known for promoting cell proliferation and vascularization. Prior research by Feng et al. [180] demonstrated that IGF-1C hydrogel provided a scaffold for adipose-derived stem cells, enhancing their survival rate and ultimately improving the therapeutic outcomes in a mouse model of acute kidney injury. Therefore, YongYao et al. [181] hypothesized that the binding of the C-terminal domain of IGF-1 to chitosan hydrogel could enhance the survival rate of human placenta-derived mesenchymal stem cells (hP-MSCs). Through in vitro and in vivo experiments, the results revealed that CS-IGF-1C hydrogel exhibited excellent biocompatibility, promoted stem cell proliferation, reduced oxidative stress-induced cell apoptosis, significantly increased cell survival rates, enhanced the pro-angiogenic effects of hp-MSCs, regulated the expression of fibrosis-related gene caspase-9, attenuated left ventricular remodeling, and improved left ventricular contractile function post-infarction. This study provides further supporting evidence for natural hydrogel carriers in stem cell therapy for myocardial infarction.

MSCs have been recognized for their role in aiding the recovery from damage caused by myocardial infarction through paracrine effects. An early study indicated that the cardiac phenotype of MSCs may influence the therapeutic efficiency. Currently, there are two approaches to stimulate the formation of a cardiac phenotype in MSCs conducive to myocardial repair—one involves exogenous additives, and the other involves non-exogenous supplementation, specifically co-culturing with myocardial cells or differentiated cardiomyocytes. With the development of tissue engineering techniques, electrically active gold nanoparticles have been widely incorporated into tissue scaffolds. Silk fibroin (SF) and chitosan (CH) exhibit excellent biocompatibility and controllable degradability, making them suitable for drug carriers in tissue engineering. Building on these foundations, Zheng Wu et al.[182]co-cultivated cardiomyocyte-like cells (H9C2) with MSCs to stimulate the development of an in vitro cardiac phenotype (Fig. 7A). Additionally, their focus was on the use of injectable electrically active gold nanoparticles loaded hydrogel, co-cultured with cardiomyocyte-like cells (H9C2) and MSCs, aiming to investigate whether it could improve cardiac tissue repair after myocardial infarction. The results indicated that, after 2 weeks of treatment with the hydrogel injected into the infarcted area, the co-culture of MSCs and H9C2 with Au@CH-SF hydrogel showed improvements in EF and FS compared to the control group, suggesting the hydrogel's efficacy in cardiac tissue repair. Furthermore, co-culturing MSCs with H9C2 using Au@CH-SF hydrogel promoted the overexpression of connexin 43 in the infarcted area, a crucial factor for cardiac tissue recovery. In this work, they innovatively utilized injectable Au@CH-SF hydrogel and co-cultured MSCs with H9C2, effectively enhancing the development of MSCs' cardiac phenotype, reducing inherent electrophysiological disturbances, and releasing bioactive factors beneficial to the heart. In conclusion, based on their research findings, the co-culture of MSCs and H9C2 with Au@CH-SF hydrogel provides a novel therapeutic strategy for cardiac tissue engineering experiments.

Chitosan (CH) is a natural polysaccharide derived from crustaceans. It is the only natural cationic polysaccharide with multiple activities, including antioxidation, anti-inflammatory, antitumor, antibacterial, and immune regulation. CH has excellent biocompatibility and biodegradability, and is an ideal biomaterial for preparing hydrogels. As was previously mentioned, the early stage of myocardial infarction is significantly influenced by the activation of inflammatory factors. Myocardial infarction is accelerated by activated inflammatory factors, particularly the buildup of interleukin IL-1β, IL-6, and reactive oxygen species. To protect myocardial tissue, it is crucial to successfully reduce the inflammatory response; otherwise, the reaction will worsen, further harming the tissue, and finally resulting in cardiac remodeling and a reduction in cardiac function. Pyroptosis of cardiomyocytes is thought to be a unique type of programmed cell death brought on by the activation of caspase-1 by the body's inflammatory response, which activates the inflammasome of caspase-11 domain 3 (NLRP 3), and the activation of NLRP3 protein hydrolysis promotes the cleavage of caspase-1 precursor. Subsequently encourage the release of inflammatory mediators and trigger cell pyrosis [183–185]. According to studies, mesenchymal stem cells are a viable therapeutic approach since they not only have the capacity for self-renewal but also have a potent immunomodulatory function that can reduce cell pyrodeath and control inflammatory reactions [186]. The applicability of stem cell transplantation is severely constrained by the extremely poor survival rate following the procedure. The researchers [187] created an acute myocardial infarction model in mice by permanently ligating the anterior falling branch of the left coronary artery, and they employed natural hydrogel chitosan as a cell transporter because of its perfect biocompatibility, biodegradability, and acceptable mechanical qualities. Through both in vitro and in vivo tests, it was demonstrated that bone marrow-derived mesenchymal stem cells greatly enhanced heart function. Control of the inflammatory microenvironment while promoting neovascularization. The development of bone marrow stem cells coated with chitosan hydrogels offers new perspectives on useful uses for the

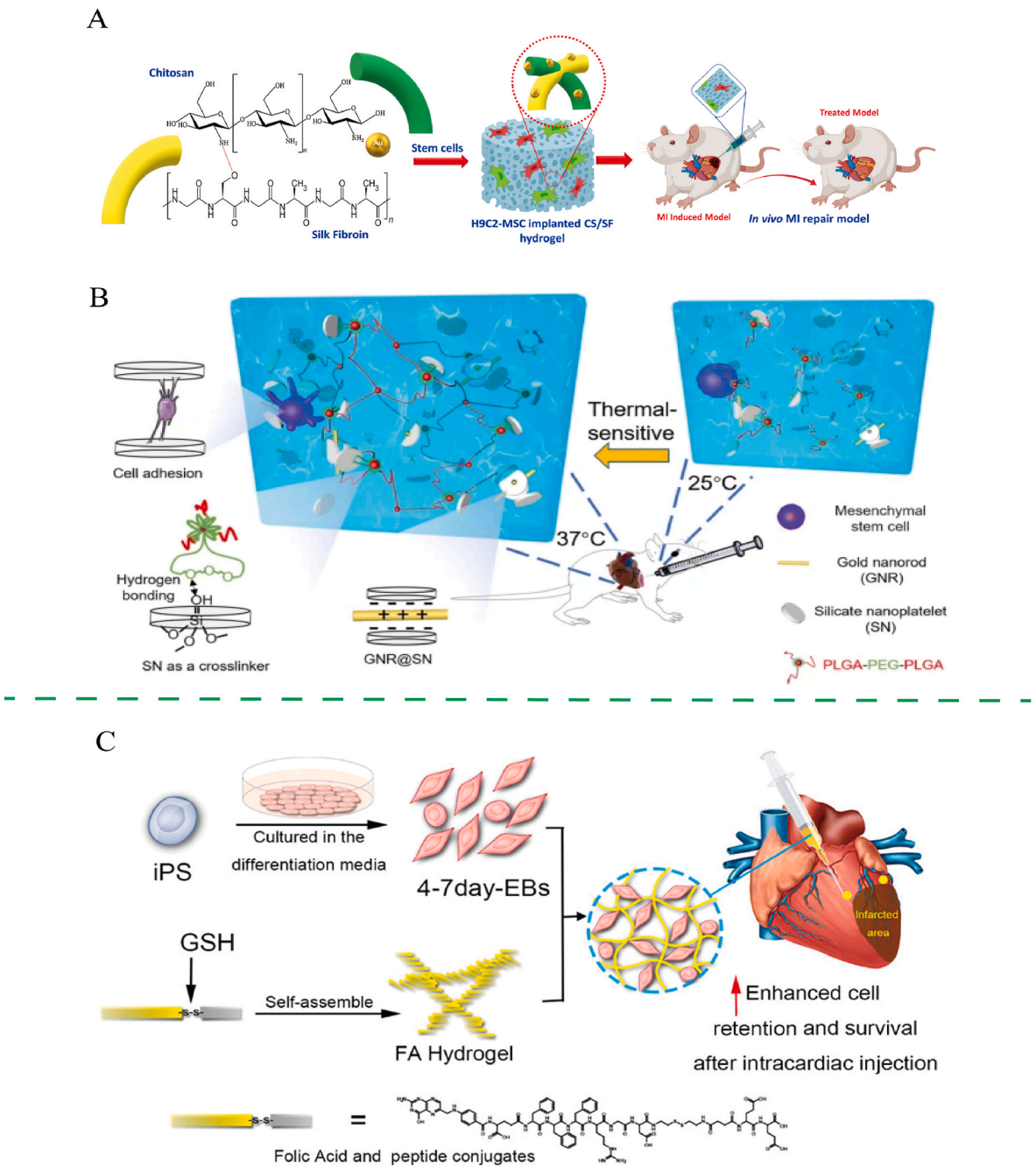

Fig. 7. Schematic diagram of stem cell-loaded hydrogel for remodeling in the post-myocardial infarction phase. (A) Therapeutic strategy of mesenchymal stem cell-loaded chitosan hydrogel for myocardial infarction. Adapted by permission [182]. Copyright © 2022 Published by Elsevier Inc. (B) Mechanism of action for the synergistic therapy of myocardial infarction using conductive nanocomposite hydrogel and mesenchymal stem cells. Adapted by permission [191]. Copyright © 2023 BioMed Central Ltd unless otherwise stated. (C) Combining iPS with FA hydrogel for myocardial infarction treatment, with the aim of enhancing stem cell survival and improving cardiac function. Adapted by permission [196]. Copyright © 2018 American Chemical Society.

treatment of myocardial infarction. We believe that bone marrow mesenchymal stem cells inhibit inflammation through a paracrine mechanism, thus reducing vascular endothelial cell death. This is crucial for treating the remodeling stage of myocardial infarction and offers a new approach for clinical treatment.

In addition, MSCs express connexin 43 (CX43). CX43 forms a functional gap link with cardiomyocytes to make up for the excessive deposition of collagen after myocardial infarction, resulting in a decrease in CX43 content and abnormal heart rate [188]. To establish syncytial structures, control arrhythmia substrates, and enhance electromechanical coupling with the heart tissue, MSCs are injected into the infarct location. According to the literature, MSCs combine with conductive biomaterials and are injected into the site of myocardial infarction [189,190]. The level of CX43 in the body is up-regulated and the differentiation of cardiomyocyte-like cells is promoted. Therefore, the use of MSCs in conjunction with conductive materials may significantly affect how myocardial infarction is treated. Based on these ideas, Zhu et al. [191] used gold nanorods (GNRs) to synthesize silicate nanosheets (SNs), poly (lactic acid-co-ethanol) -b-poly (ethylene glycol) -b-poly (lactic acid-co-ethanol) (PLGA-PEG-PLGA), and encapsulated MSCs (Fig. 7B). GNR @ SN/Gel hydrogel was directly injected into the myocardial infarction area of rats. They observed that MSC-loaded

injectable hydrogel reduced the I/III collagen ratio, which effectively prevented the process of cardiac pathological remodeling. In summary, the novel MSCs-loaded conductive injectable hydrogel improves electromechanical coupling, protects cardiac viability, and improves cardiac function.

In early research, it was shown that MSCs can increase cell survival rate, promote paracrine factor secretion, and promote angiogenesis in vitro and in vivo [192]. Therefore, MSCs-based paracrine chemical therapy has become a potential treatment strategy for myocardial infarction; however, it has a poor therapeutic impact because the blood flow quickly removes it and only a small amount builds up in the heart tissue [193]. Based on the above shortcomings, a novel injectable Ang-1 thermosensitive hydrogel (Ang-1 gel) was created by Hu team [194] to enable the sustained administration of MSC exosomes. Ang-1 gel was injected into MI mice. Compared with ISL1-MSCs-Exo alone, Ang-1 gel promoted the proliferation and anti-apoptosis of exosomes and, improved heart function and myocardial fibrosis after MI. It is worth mentioning that thermosensitive hydrogel-encapsulated Ang-1 induces angiogenesis and maturation, and has a synergistic therapeutic effect with ISL1-MSCs-Exo, providing a new therapeutic strategy for promoting tissue regeneration after ischemic injury. However, this study had some limitations. It is necessary to clarify the relationship between ISL1-MSCs-Exo and Ang-1 hydrogels in more detail. The results showed that the Ang-1 hydrogel improved the biological functions of exosomes. Further research is necessary to determine whether these effects are brought on by the Ang-1 hydrogel's overlapping biological activities or by an increase in exosome content, to better apply these findings to the treatment of myocardial infarction during the remodeling phase.

MSCs have cardiomyocyte-like characteristics and cannot differentiate into fully mature functional cardiomyocytes. Moreover, the environment in the infarcted area is harsh, and it is difficult for MSCs to survive. Therefore, the current study suggests that MSCs repair the myocardium mainly through paracrine production of active growth factors, and act on adjacent cells to improve the microenvironment of the infarct area, inhibit myocardial fibrosis, and promote injury repair. An increasing number of studies have shown that hydrogels combined with MSCs can significantly promote the effect of MSCs in the treatment of MI, however, optimal dose of MSCs, optimal route of administration and selection of biological materials still require further study. In conclusion, MSCs have become important candidate cells for repairing damaged myocardial tissue, and optimization strategies for the treatment of MI are gradually being studied. We believe that with scientific progress, loaded MSCs hydrogels will benefit most patients with myocardial infarction.

6.1.2. Inducing pluripotent stem cells loaded hydrogel

iPSCs are pluripotent stem cells obtained by reprogramming and inducing adult cells. They can differentiate into multiple cell types, providing new hope for the regeneration and repair of myocardial infarction [195]. Poor microenvironment after myocardial infarction leads to low retention and survival rates of induced pluripotent stem cells. Therefore, the repair of cardiac function by iPSCs is believed to benefit from a paracrine effect. To improve the survival rate of iPSCs in vivo and prolong their action time, researchers have combined iPSCs with hydrogels to develop new strategies for the treatment of myocardial infarction.

Li et al. [196] designed and synthesized a folic acid (FA) monomer supramolecular hydrogel containing a diphenylalanine sequence, in which the FA monomer formed a stable tetramer through hydrogen bonds. They dispersed self-differentiated iPS cell ovules into single cells and labeled them. The mouse heart was injected with a hydrogel containing labeled iPS single cells immediately the left anterior section of the coronary artery was severed. The results showed that the implantation rate of FA hydrogel cells loaded with iPS cells was approximately three times that of the iPS group, and the FA hydrogel + iPS group had the greatest heart function in the MI hearts, which was consistent with the results of the histological analysis. Notably, the FA hydrogel + iPS group effectively reducing the degree of myocardial fibrosis and ventricular remodeling. In addition, they noticed that the transplanted cells in the FA hydrogel + iPS group facilitated CM differentiation and neovascularization, and offered significant potential for treating myocardial infarction. In 2017, Chow et al. [197] investigated the therapeutic effects of polyethylene glycol hydrogel (PEG), erythropoietin (EPO), and cardiomyocytes derived from human induced pluripotent stem cells (Ipsc-CMs) in rats with myocardial infarction. EPO, also known as a cardioprotective molecule, has been clinically proven to have significant benefits in cell death and remodeling after myocardial infarction [198]. Ten weeks after, the injection of iPS-CM and EPO-loaded PEG hydrogel into the infarcted heart, ventricular remodeling in the experimental group was weakened, the ejection fraction was significantly increased, the thickness of myocardial infarction and muscle content were increased, and heart failure was effectively prevented.

Induced pluripotent stem cells (hiPS) represent a pluripotent cell lineage obtained through the reprogramming of adult somatic cells, akin to human embryonic stem cells. In recent years, the regenerative potential of hiPS in the context of myocardial infarction has been substantiated through studies in small animal models [199,200]. The expression of gap junction proteins in hiPS-derived cardiomyocytes (hiPS-CMs) is relatively diminished, resulting in limited functional integration with the host myocardium and impeding contraction functionality [201]. Consequently, strategies for myocardial infarction treatment based on hiPS-CMs necessitate further optimization. Hyaluronic acid (HA) is characterized by excellent biocompatibility and low immunogenicity, rendering it widely employed in the functionality of cardiac tissue. Moreover, HA can be modified with certain functional groups, such as thiol and amine, endowing it with specific reaction sites. In the research conducted by Hekai Li [202], they incorporated multimodal nano-

sized gold nanoparticles (AuNPs) into hydroxyapatite (HA), conferring appropriate rigidity, mechanical strength, and electrical conductivity to HA. This study aimed to further elucidate whether the AuNP-HA hydrogel encapsulating human-induced pluripotent stem cell-derived cardiomyocytes (hiPS-CMs) could establish improved connections within myocardial tissue and enhance functional recovery following myocardial infarction. Permanent ligation of the left anterior descending coronary artery was performed in mice, and the hydrogel was injected into two symmetrical sites within the myocardium surrounding the infarct after the ischemic event. The results demonstrated that the AuNP-HA hydrogel, by promoting the formation of gap junction protein CX43, improved the contractile function and electrophysiological activity of hiPS-CMs. To further investigate how the hydrogel enhanced gap junctions, Western blotting confirmed that it occurred through the integrin/ILK1/p-AKT pathway. Encapsulation of hiPS-CMs with AuNP-HA hydrogel post-myocardial infarction significantly improved cardiac function, inhibited left ventricular infarct size, proliferation of scar tissue, and collagen deposition, effectively impeding myocardial fibrosis. Furthermore, hiPS-CMs exerted a protective effect on the heart by promoting vascular regeneration in the infarcted area through paracrine actions. While this study optimized the strategy for treating myocardial infarction with hiPS-CMs, it also has certain limitations. Firstly, the use of a mouse model may lack clinical relevance due to substantial phenotypic differences between human and murine myocardial cells, necessitating validation in larger animal models. Secondly, the observation period in this study was insufficient to determine potential immune rejection reactions, requiring a longer follow-up assessment time.

In another study, Wang et al. [203] coupled a hydrogel with a collagen-binding peptide (SYIRIADTNIT) to achieve a sol-gel phase transition at 37 °C in vivo and showed a strong affinity for type I collagen. Therefore, they predicted that the hydrogel can be well combined with the infarcted area to immobilize the induced pluripotent stem cells (iPSCs) encapsulated in it into the damaged myocardium. Two weeks after injection, results showed that cardiac function was

significantly improved, ventricular dilatation and fraction shortening were reduced, and poor ventricular remodeling was alleviated. The temperature-sensitive hydrogel not only improves the survival rate of iPSCs and ensures that cells can play a role in repairing the heart, but also forms a gel shape according to the change in body temperature, providing support for the infarct area to achieve the purpose of treating MI.

In the above experiments, hydrogel-loaded induced pluripotent stem cells have a good repair effect on cardiac function after myocardial infarction, which may benefit from the paracrine effect for iPSCs. Ideal hydrogel properties of iPSCs include excellent degradability, biocompatibility, and effective cell adhesion.

6.1.3. Embryonic stem cells loaded hydrogel

Embryonic stem cells (ESCs) are an important cell source in regenerative medicine. They have the potential for proliferation and specific differentiation, and can theoretically differentiate into all tissue cells in the body. Since ESCs promote myocardial regeneration, encouraging results have been achieved in MI treatment. The mechanism of ESC-based myocardial cell treatment is remains complicated, and there is a need for improvements in cell delivery and implantation.

Injectable matrix metalloproteinase (MMP) reactive functional hydrogels were created by Krarhenbuehl et al. [204] as scaffolds, and thymosin b4 (Tb4) and human embryonic stem cells (hESC) which encourage angiogenesis were wrapped in the hydrogels. The hydrogel replaced the degraded extracellular matrix in rat myocardial infarction and slowly released encapsulated Tb4 and hESC. Magnetic resonance imaging demonstrated that Tb4 and hESC combined with the bioactive hydrogel successfully preserved the systolic function of the heart in a short period of time after myocardial infarction in rats, weakened the degree of left ventricular dilatation, and decreased the area of myocardial infarction. Additionally, there was an increase in the vascular density of the infarcted tissue, which may have been caused by an elevated pro-angiogenic cytokine concentration in the blood.

To improve cardiac remodeling and myocardial infarction function, Wang's lab [205] has created injectable biodegradable oligomeric [polyethylene glycol fumarate](OPF) hydrogel composites. In the physiological environment of the body, OPF is crosslinked by free radical initiators to form hydrogels, and is degraded in vivo and in vitro by the hydrolysis of ester groups [206,207]. The team loaded ESCs onto the OPF hydrogel and performed injection surgery one week after myocardial infarction. After four weeks of implantation into the myocardial infarction model, crucially, exceeded that of the control group, and the cell retention and survival in the ischemic myocardium after transplantation were improved. These results demonstrated that under ascorbic acid induction, ESCs in the OPF hydrogel maintained their ability to differentiate into specific cell types in-vitro. In light of the foregoing findings, OPF hydrogel was employed as a vehicle for delivering of embryonic stem cells in order to treat MI.

Although the use of hydrogels infused with embryonic stem cells in myocardial infarction offers a fresh perspective on bioengineering, there are few studies on this particular hydrogel, necessitating further investigation.

6.2. MicroRNAs loaded hydrogel

MicroRNAs, abbreviated as miRNAs, are single-stranded non-coding RNAs typically consisting of 20–25 nucleotides. The miRNA family is a tool for cardiac tissue engineering repair because it targets various mRNAs to regulate numerous downstream pathways in the body. It interferes with signals to inhibit complementary messenger RNA (mRNA) [208,209]. According to reports [210], miRNAs play a crucial role in regulating apoptosis and cell survival. Increasing the number of miRNAs associated with cell survival can enhance tissue repair at the site of myocardial infarction. So far, several MiRNA families have been identified as MI-related, including anti-cardiomyocyte apoptosis MiRNAs [211,212] such as MiRNA-24 and MiRNA-214, promoting cell proliferation MiRNAs [213,214] such as MiRNA-19, MiRNA-199a-3p, MiRNA-590, and promoting angiogenesis MiRNAs [215] such as MiRNA-210. Additionally, MiRNAs associated with myocardial infarction repair can stimulate tissue repair through their paracrine signals.

Disappointingly, delivering and retaining miRNAs at the site of myocardial infarction pose significant challenges. Free miRNAs are susceptible to degradation by endogenous ribonucleases with short half-life and off-target effect, so it is impractical to directly deliver naked miRNAs [216]. To address this issue, researchers have explored various chemically modified miRNAs, including adding sulfur bonds [217]and adding fluorine atoms [218] to the structure. Although group modification can prolong the half-life of miRNAs, these modifications still cannot solve the off-target effect and toxic by-products. Based on the characteristics of low cytotoxicity, high stability, and controllable release, injectable hydrogels have been employed as biological carriers for MiRNA delivery to protect bare MiRNAs, making it more targeted for transport.

6.2.1. miRNA-199a-3p loaded hydrogel

The previously mentioned miRNA-199a-3p is involved in the repair and treatment of ischemic hearts. It stimulates cardiomyocyte proliferation through the molecular targets of HOMER1 and CLIC5, and activates p-AKT signaling through carvedilol to protect cardiomyocytes from ischemia-reperfusion injury [219]. For the clinical application of miRNA-199a-3p, researchers initially used an adeno-associated virus (AAV) for transmission. MiRNA-199a-3p packaged with AAV was injected intraperitoneally into an animal model of myocardial infarction [220]. The results showed that it promoted cardiomyocyte proliferation and restored infarcted myocardial function. Although AAV has achieved effective transfection, its use has been constrained by the possibility of an immune reaction, long-term transgenic expression, and lack of space-time control [221].

Polymer nanoparticles (NPs) were employed by Yang et al. [222] as miRNA carriers (miNPs), loaded them into shear-thinning hydrogels, and labeled the miNPs with biocompatible fluorescent conjugated polymers (PFBT) to accurately track them. In this study, a second cell penetrating peptide (CPP) was added to the miNPs shell to increase the transfection effectiveness of miRNAs in cardiovascular cells, guarantee that these cells efficiently absorb the miRNAs, and ensure maximum release of miRNAs. The delivery system was injected into the myocardial infarction model to achieve local minimally invasive injection, and the released local miNPs interacted with CMs to promote CMs proliferation, significantly improve cardiac function, reduce fibrosis scars, and increase vascular density. The high biocompatibility and transfection efficiency of miRNA delivery systems have been demonstrated in both in vivo and in vitro ischemic models. On this basis, the team stained left ventricular tissue sections, and found that the hydrogel could be stably implanted in the experiment, with no obvious changes. A single dose of the miNP-loaded hydrogel significantly and continuously restored the infarcted myocardium through neovascularization for up to three months. Myocardial infarction therapy in the future has great potential as miRNA delivery method created by Yang's team.

6.2.2. miRNA-196c-3p loaded hydrogel

Unlike apoptosis, necroptosis, and other types of cell death, ferroptosis is iron-dependent and controlled. Heart failure may lead to myocardial hemorrhage, resulting in the release of free iron into the myocardium, followed by MI left ventricular remodeling [223]. According to literature, the central genes that regulate ferroptosis in the body are NOX4, P53 and LOX. Therefore, researchers are working to identify miRNAs that target genes that regulate ferroptosis to improve cardiac function following MI [224–226].

According to a prediction made by Jingjing Ji laboratory [227], MiRNA-196c-3p concurrently controls the expression of genes associated with ferroptosis. To achieve this, the team developed a novel type

of photosensitive dynMIc covalent gel composed of a fructose polymer (PFA) as well as BOB polymer (PANB), which are connected by dynMIc covalent bonding. To create an injectable gel with NIR-II light-triggered release (mimics + Gel/BTN), they also loaded photothermal nanoparticles (BTN) and MiRNA-196c-3p mimics on the hydrogel. The group found that at 1064 nm laser could be used to turn on or off the release of mimics via mimics + Gel/BTN. Researchers constructed a rat I/R model and completely covered the infarct area with mimics + Gel/BTN. The survival curve OF the 28-day I/R mode was plotted, and they found that the group of I/R + mimics + Gel/BTN had a considerably higher survival rate than the other experimental groups. The I/R + mimics + Gel/BTN group exhibited less fibrosis than the other experimental groups, according to Masson staining. Additionally, quantitative analysis of associated proteins showed that mimics + Gel/BTN could effectively target the NOX4, P53, and LOX genes in situ. As a result, mimics + Gel/BTN which target genes associated with apoptosis, enhanced cardiac muscle function, prevented cardiomyocyte apoptosis, and increased survival rates in I/R rats.

An increasing number of miRNAs with various biological activities are being discovered due to advancements in technology [228], opening up a new area of therapy for heart disease. This opens up a new area of therapy for heart disease. This direction is full of value and opportunity, and is worth exploring.

7. Hydrogel-based cardiac patch

A "heart patch" denotes a polymer porous scaffold or hydrogel that is affixed to the damaged site of the myocardium through suture fixation or spontaneous adhesion. Natural materials (such as proteins, alginates, etc.) and synthetic biopolymer materials are widely used in the preparation of cardiac patches by electrospinning, electrowetting and 3D printing [229,230]. Cardiac patches have demonstrated their therapeutic advantages in the treatment of myocardial infarction, serving as a delivery platform for therapeutic stem cells, bioactive substances, etc.

Most adhesive patches are irreversible, making it difficult to remove them from damaged tissue and potentially causing further harm. Therefore, constructing a reversibly adhesive hydrogel patch that can be removed on demand is both crucial and necessary. Janus hydrogels, with their asymmetric characteristics, hold immense potential in tissue engineering. Current research related to asymmetric hydrogels

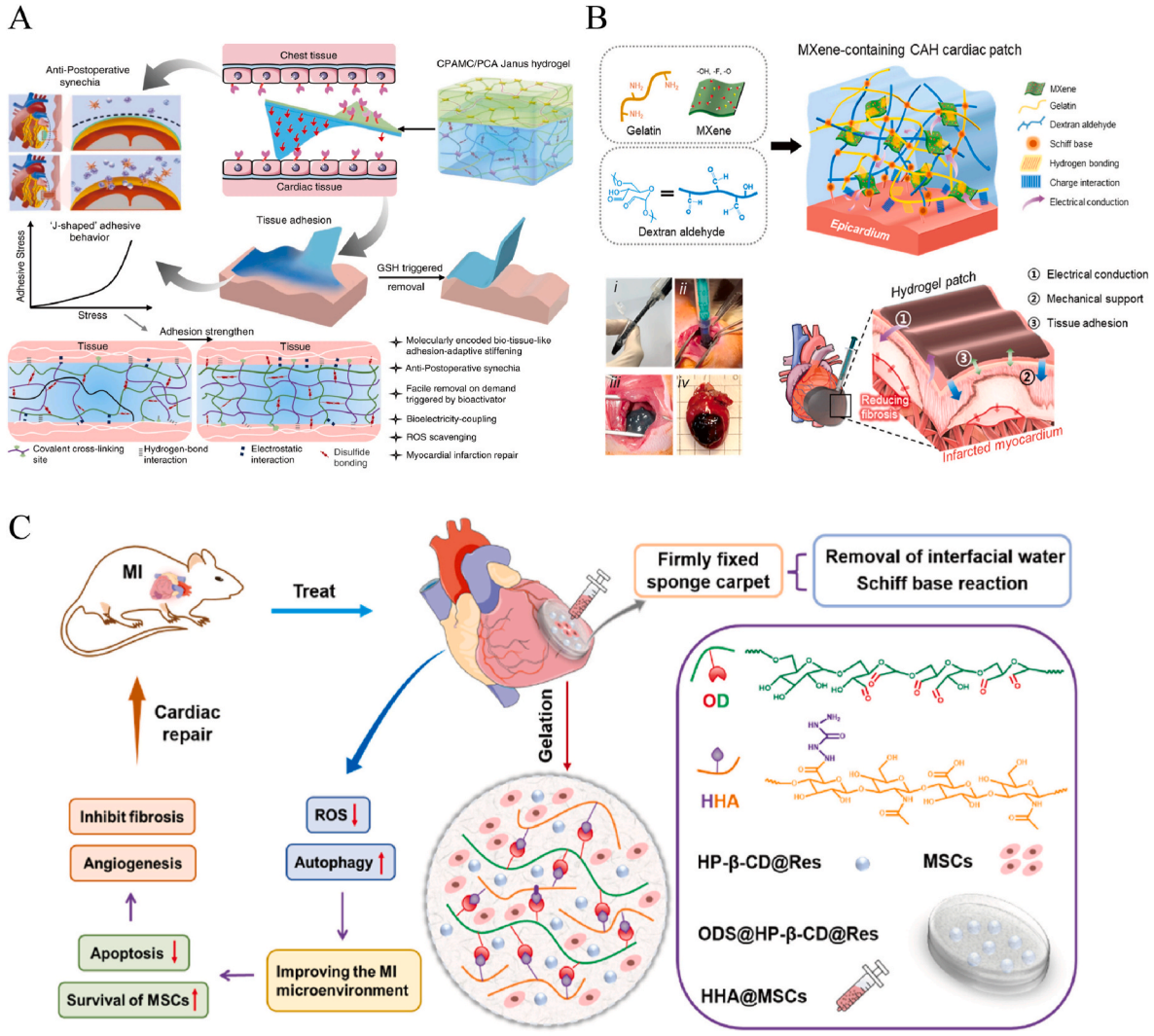

Fig. 8. Schematic illustration of the application of cardiac patches in myocardial infarction.(A) The CPAMC/PCA Janus hydrogel exhibits asymmetry, allowing for rapid adherence to moist cardiac tissue and detachment triggered by on-demand stimulation, effectively preventing postoperative adhesions. Adapted by permission [231]. Copyright © 2023 Springer Nature Limited. (B) The fabrication process of electrically conductive adhesive cardiac patches using MXene and their potential therapeutic effects on myocardial infarction. Adapted by permission [232]. Copyright © 2023 American Chemical Society. (C) Mechanism of action for a wet-adhesive cardiac patch containing antioxidant, autophagy-regulating molecular capsules, and MSCs in the treatment of myocardial infarction. Adapted by permission [240]. Copyright © 2022 The Authors.

primarily focuses on treating gastric perforations and preventing post-operative adhesion formation. Due to the complexity and high difficulty of cardiac tissue engineering, developing a Janus hydrogel that can repair cardiac function after myocardial infarction and detach from the tissue on demand to prevent tissue adhesion remains a significant challenge. Oxidative stress and inflammation activation are key mechanisms in the early stages of myocardial infarction. After myocardial infarction, macrophages are rapidly activated into M1 type, secreting inflammatory factors that lead to damage in myocardial tissue. Most adhesive hydrogels currently mainly address adhesive properties, paying little attention to whether they can reduce the inflammatory levels of myocardial infarction tissue. Therefore, He [231] innovatively constructed an asymmetric Janus hydrogel patch to prevent post-operative adhesion. The patch consists of two layers, with the top layer having anti-cell adhesion properties, effectively preventing post-operative tissue adhesion (Fig. 8A). In contrast, the bottom hydrogel layer can stably adhere to cardiac tissue and be removed on demand. Additionally, they endowed the patch with excellent conductivity, anti-inflammatory, and antioxidant properties. This multifunctional Janus hydrogel patch holds great promise in overcoming the limitations of current cardiac patches. The results indicate that in the experimental group treated with Janus hydrogel, CD68-positive cells decreased, and CD206 cells increased, suggesting that macrophages mainly exist in the M2 type, demonstrating excellent anti-inflammatory effects. ROS is a crucial factor promoting apoptosis and necrosis of cells after myocardial infarction. Janus hydrogel exhibits excellent anti-ROS capabilities, effectively maintaining the physiological function of CMs and inhibiting ventricular remodeling. They also used anti-vwf antibodies to label microvessels and found that the Janus hydrogel group in the infarct area promoted the formation of new blood vessels, with clear arterial structures and increased density. In summary, this study pioneered the development of a multifunctional Janus hydrogel patch with on-demand removal, providing evidence that it can alleviate inflammation and ROS levels in the infarct area, effectively preventing adhesion between the infarct area and other tissues, offering a new perspective on treating myocardial infarction.

Traditional cardiac patches require surgical sutures, which may lead to further inflammation and bleeding. After myocardial infarction, the substantial death of myocardial cells and collagen deposition obstructs the electrical pulse signals in cardiac tissue. Therefore, there is a need to develop a cardiac patch with biocompatibility, excellent adhesion, and high conductivity. In a study, Mingyu Lee and colleagues [232] utilized MXene combined with gelatin. MXene is a transition metal carbide/nitride with a conductive layered structure, widely used in various biomedical applications (Fig. 8B). Notably, MXene, unlike other conductive materials, is hydrophilic and can be mixed with hydrophilic polymers. Gelatin hydrogel has high biocompatibility, providing good mechanical support in the infarcted area. The principle behind the combination of MXene and gelatin is that these polymers can undergo gelation through Schiff base reaction, allowing them to adhere to the epicardium. Through in vivo and in vitro experiments, it was observed that this cardiac patch, after 7 days of action on cardiomyocytes (CMs), promoted the expression of CX43 in cardiac tissue and enhanced electrical coupling and signal propagation between CMs, facilitating CM maturation and improving heart function. Additionally, it induced macrophages to transition to an M2 phenotype, alleviating the inflammatory response in the infarcted area and inhibiting cell apoptosis and necrosis. Importantly, MXene did not cause systemic toxicity, demonstrating high safety. However, in future work, further elucidation of the therapeutic mechanisms of this cardiac patch is needed, providing a unique perspective for MI treatment.

Furthermore, after myocardial infarction, the extracellular matrix undergoes degradation, leading to cardiomyocyte apoptosis, the formation of fibrotic scars, and adverse remodeling, further impairing the physiological electrical conduction of myocardial cells. Combining conductive polymers (CPs) with hydrogels can partially restore electrical conduction in cardiac tissue after myocardial infarction, preventing further deterioration into arrhythmias. Traditional CPs are hydrophobic and challenging to uniformly distribute in hydrophilic hydrogels and within the body [233,234]. Moreover, the conductivity of traditional CPs comes from acid doping agents, including sulfate ions and naphthalene sulfonate ions, significantly reducing the biocompatibility of the hydrogel. Therefore, developing a cardiac patch that restores conductivity in infarcted myocardium is highly necessary. Chaojie Yu [235] used the anionic side chain of polyaniline and gelatin to construct a conductive cardiac patch (MEHP). Their design approach enhanced the hydrophilicity of the hydrogel, adjusted the conjugated skeleton, resulting in a more uniform distribution of the hydrogel network, improving the conductivity of the hydrogel patch and enhancing biocompatibility. Combining MEHP with adipose-derived stem cells (ADSCs) and injecting them into the pericardial sac of rats facilitated the repair of heart function and vasculature reconstruction after myocardial infarction, suppressing ventricular remodeling and fibrosis. Importantly, MEHP restored the electrical conduction function in the infarcted area. The safety of MEHP implantation in vivo needs further investigation to advance clinical translation, providing a new strategy for treating myocardial infarction.

Excessive ROS lead to mitochondrial damage, triggering further ROS production and establishing a vicious cycle. Currently, numerous biocompatible materials capable of scavenging ROS have been developed. However, there has been limited attention to inhibiting the generation of ROS at its source. Autophagy, a process involving the engulfment of cellular proteins or organelles and their encapsulation into vesicles, which then fuse with lysosomes to form autolysosomes, is vital for maintaining cellular homeostasis and fulfilling the metabolic needs of the cell, including the renewal of certain organelles. Autophagy has been reported to facilitate the recovery of cardiac function post-myocardial infarction [236,237]. 2-hydroxypropyl-β-cyclodextrin (HP-β-cd) is a complexing agent that enhances the water solubility and bioavailability of drugs [238]. There is currently no literature reporting the protective effects of HP-β-cd on the heart. Resveratrol (Res) is a polyphenol produced by plants, known for its antioxidant and anti-inflammatory properties. It can inhibit lipid peroxidation and regulate the antioxidant activity of related enzymes. Unfortunately, Res has poor water solubility, significantly limiting its biological functionality [239]. Building on this, Tengling Wu et al. [240] utilized HP-β-cd to improve the water solubility of Res, allowing their interaction to form molecular capsules (HP-β-cd@Res) (Fig. 8C). The aim was to activate autophagy and restore cardiac function post-myocardial infarction. Considering the unfavorable microenvironment post-MI, which hinders the retention of drugs and cells, they developed an adhesive hydrogel containing HP-β-cd@Res and mesenchymal stem cells. They prepared a wet-adhesive hydrogel (HHA@ODS) using aldehyde dextran sponge (ODS) as the raw material and encapsulated HP-β-cd@Res molecular capsules within it. They hypothesized that after injection into the body, ODS@HP-β-cd@Res could react with amino groups on cardiac tissue, anchoring it to the heart. Subsequently, a mixture of mesenchymal stem cells in HHA solution was infiltrated into ODS@HP-β-cd@Res, forming HHA@ODS@HP-β-cd@Res hydrogel through the Schiff base reaction between the remaining aldehyde hydroxyl groups on the outer layer of ODS and the hydrazine groups on HHA. This immobilized the mesenchymal stem cells loaded-HHA@ODS@HP-β-cd@Res hydrogel on the surface of the myocardium. Through a series of experiments, it was found that this hydrogel effectively scavenged ROS, activated the autophagy pathway, inhibited cardiomyocyte apoptosis, increased the retention rate of mesenchymal stem cells, and improved the cardiac microenvironment. Furthermore, mesenchymal stem cells, through paracrine effects, promoted angiogenesis, effectively alleviating myocardial fibrosis and restoring heart function. This therapeutic strategy holds promise for treating myocardial infarction and addressing clinical challenges.

Neuromodulator-1 (NRG-1), as a bioactive factor, is a signal growth

factor released by ventricular endocardium and cardiac microvascular endothelium. Studies have shown that NRG-1/ErbB signaling can effectively induce cardiomyocyte proliferation, inhibit cardiomyocyte apoptosis, and promote angiogenesis by activating ERK and AKT pathways, which can be used for myocardial repair and cardiac regeneration [241,242]. In some clinical trials, cardiac function has been significantly improved after receiving NRG-1 treatment in cardiovascular patients [243,244]. Based on the

above experimental basis, the team [245] developed a fibrin-based heart patch and loaded NRG-1 on the heart patch. Fibrin heart patch is a self-assembled biopolymer derived from fibrinogen and thrombin. It has the advantages of good biocompatibility, degradability and low immunogenicity. They constructed a mouse model of myocardial infarction and expected that the composite heart patch could significantly improve cardiac function after myocardial infarction. After a series of in vitro and in vivo experiments, the results showed that the NRG-1-loaded fibrin heart patch had good comprehensive performance, provided mechanical support for the infarct area, inhibited apoptosis after myocardial infarction, promoted cardiomyocyte proliferation and neovascularization in the infarct area, and significantly improved cardiac function. Therefore, the use of fibrin patch as a carrier to deliver active growth factors locally to the infarct area can significantly improve myocardial regeneration and has broad prospects in the clinical treatment of MI.

After MI, fibrotic scar tissue is formed in the infarct area, and these pathological tissues are non-conductive, which will cause the transmission of electrical pulses in the heart to be blocked, resulting in abnormal cardiac contraction and relaxation and the transmission of electrical signals. Researchers have incorporated conductive polymers into biomaterials to explore conductive cardiac patches. Shuang Liang 's team [246] designed a conductive heart patch that can be quickly bonded. They constructed a hyperbranched polymer with a pyrrole group of heterodopMIne, and pyrrole and dopMIne were polymerized in situ by Fe^{3+} oxidation. The complexation of dopMIne and Fe^{3+} makes the hydrogel have adhesion properties, and pyrrole polymer as a conductive material gives the hydrogel conductivity. The hydrogel patch was uniformly coated in the infarcted area. After four weeks of close combination, the infarcted myocardium's revascularization and cardiac function reconstruction both improved. Additionally, electrophysiological signal transmission was successfully enhanced.

In recent years, cardiac patches have shown remarkable promise in mending myocardial injuries. However, their clinical application continues to face challenges. On one hand, the current research on cardiac patches is still not exhaustive. For example, after long-term implantation of conductive cardiac patches into the heart, the physiological toxicity of conductive materials, including inorganic nanomaterials and metal ions, needs to be further studied and explored by researchers, and there are few reports on the complete matching of the conductivity of cardiac patches with the conductivity of host myocardial tissue. On the other hand, compared to the minimally invasive injection of hydrogels, the implantation of cardiac patches requires thoracotomy, which inevitably heightens intraoperative risks for patients. It may lead to postoperative inflammation and pericardial adhesions, prolonging patient recovery times and potentially increasing the incidence of complications and mortality.

8. Conclusion and prospect

One of the main illnesses that endanger people's health is myocardial infarction. At present, conventional clinical treatments are plagued by repeated administration and acute nephrotoxicity. With the emerging development of cardiac regenerative medicine and bioengineering, hydrogel, as an important biomaterial, has good swelling and absorption capacity, and has high affinity with body tissue. After being modified by various methods, as a delivery system, it shows a breakthrough in the field of cardiac biomaterials and shows great application prospects. Hydrogel offers two distinct advantages in the treatment of myocardial infarction compared to other materials: on the one hand, it provides mechanical support for the ventricular wall. The three-dimensional skeleton structure of hydrogel can improve cardiac function by increasing ventricular wall thickness, reducing ventricular stress, limiting systolic tension and improving myocardial remodeling. On the other hand, hydrogels further exert their therapeutic and restorative functions by mimicking extracellular matrix and myocardial microenvironment. Hydrogel can well simulate the extracellular matrix, reduce the expression of inflammatory factors, inhibit cell apoptosis, thereby inhibiting myocardial fibrosis, and extend the time of the function of loaded substances (including stem cells, bioactive factors, etc.) in the myocardium. Understanding the physiological and pathological mechanisms following myocardial infarction is essential for the development of new biomaterials. By combining the pathological mechanism with the material, a more suitable local treatment for the heart is developed. In recent years, researchers have modified the chemical structure of hydrogels according to the pathogenesis of myocardial infarction, and developed various types of injectable hydrogels. It is important to note that injectable hydrogels are functional biomaterials with therapeutic responses, utilized to encapsulate a variety of therapeutic compounds, and are appropriate substitutes for myocardial infarction tissues. They have been deemed by researchers to be almost perfect ECM counterparts. Thoracotomy is not an option for people with mild to severe heart failure. Minimally invasive injection of injectable hydrogels gives them hope, reduces the formation of fibrotic scars, inhibits left ventricular dilatation, and significantly improves cardiac function.

As a new kind of biomaterial, hydrogel has developed rapidly, from traditional wound dressings to contact lenses and various types of loaded hydrogels that have developed rapidly in recent years. The entry of hydrogels from the laboratory to the clinic requires relevant supervision and approval. The regulations and guidance for the regulatory process of hydrogel products are constantly updated. Here, the author takes FDA as an example to illustrate the regulatory approach of hydrogels. If the hydrogel is not formed by a chemical reaction, it can usually be approved as a medical device. If the hydrogel is used as a carrier and is loaded with related therapeutic drugs, stem cells, etc., such hydrogels require a new drug application (NDA), a biological license application (BLA), or a device approval/license to market. Most hydrogels can be divided into three categories according to the risk level of medical devices [247]. Class III high-risk hydrogel medical devices require pre-market approval (PMA). Similar to NDA nuclear BLA, PMA is one of the most stringent regulatory controls in the FDA, requiring researchers to obtain a large amount of preclinical and clinical data to prove the safety and effectiveness of the biomaterial. The safety risk of class II hydrogel medical products is relatively small, and its clinical approval is mostly based on proving that its effectiveness and safety are equivalent to known approvals. Class I hydrogel medical products refer to devices that are not used to maintain life, mainly including various wound excipients. This is also the most classic clinical application of hydrogels. Generally, it does not require pre-market approval and notification, but it still needs to meet the relevant drug production quality management specifications (GMP). A prudent and rigorous regulatory process is an absolute and necessary condition for ensuring patient safety. However, the threshold for the transformation of new hydrogels from laboratory to clinical is still high. These difficulties mainly come from two aspects: on the one hand, the long time and high cost of research and development, production and approval of hydrogels, on the other hand, the challenges from the production and storage process of hydrogels themselves. With the development of biomaterials engineering, in order to better meet the needs of clinical treatment, the regulation of new hydrogels is also crucial.

Challenges and opportunities coexist. Although hydrogels for cardiac tissue engineering have made outstanding progress, many challenges still need to be addressed before these methods can be safely used in clinical practice. For example, the choice of materials for cardiac repair,

injection dose, timing of injection, and distribution of materials are key factors that need further study. Consequently, preclinical studies should be conducted in large animal models with physiological activities similar to the human heart. These studies need to cover long-term results and carefully observe the body 's response after long-term injection. The related safety problems and mechanism of action after hydrogel injection also need to be studied, such as how to solve the problem that the injected hydrogel is injected in the wrong position or cannot reach the specific tissue accurately. In addition, to make hydrogels have sufficient safety, effectiveness, and ideal regulatory approval and clinical use evidence, biomaterials scientists, chemists, and biologists need to work together to gradually reduce the threshold of clinical conversion of hydrogels, and further expand the scope of clinical application of hydrogels. It is anticipated that, in the near future, injectable hydrogels and heart patches will bring increased hope and confidence to a growing number of myocardial infarction patients, ultimately benefiting their well-being.

CRediT authorship contribution statement

Qiaxin Xu: Methodology, Software, Writing – original draft, Writing – review & editing. **Zeyu Xiao:** Writing – original draft. **Qianzhi Yang:** Supervision. **Tingting Yu:** Writing – original draft. **Xiujiao Deng:** Supervision. **Nenghua Chen:** Methodology. **Yanyu Huang:** Supervision. **Lihong Wang:** Funding acquisition. **Jun Guo:** Funding acquisition. **Jinghao Wang:** Funding acquisition, Writing – review & editing.

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.

Data availability

The data that has been used is confidential.

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List of abbreviations

MI: myocardial infarction
ECM: extracellular matrix
CH: Chitosan
LCST: lowest critical phase transition temperature
HGF: hepatocyte growth factor
BASCs: brown adipose-derived stem cells
ROS: reactive oxygen species
CAT: catalase
eNOS: endothelial nitric oxide synthase
iNOS: inducible nitric oxide synthase
EF: ejection fraction
FS: fraction shortening
LVIDd: left ventricular end-diastolic diameter
VNS: Vagus nerve stimulation
SPIO: Superparamagnetic iron oxide
bFGF: basic fibroblast growth factor
VEGF: Vascular endothelial growth factor
IGF-1: Insulin-like growth factor 1
MSCs: mesenchymal stem cells
ESCs: Embryonic stem cells
hESC: human embryonic stem cells
AAV: adeno-associated virus
NRG-1: Neuromodulator-1