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Multifunctional applications of hydrogel materials in myocardial infarction treatment: from tissue repair to microenvironment regulation

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Myocardial infarction (MI) is one of the leading causes of heart failure and death worldwide. While conventional treatments have limitations in promoting myocardial repair and regeneration, hydrogel, as a multifunctional biomaterial, shows great potential in MI treatment due to its unique physicochemical properties and biocompatibility. This paper reviews the multifunctional applications of hydrogels in MI therapeutics, including drug delivery (miRNAs, exosomes, *etc.*), electrical conduction, immunomodulation, detection, tissue engineering, and microfluidic functions. In terms of drug delivery, hydrogels are able to precisely deliver drugs, stem cells and exosomes to improve the microenvironment of the infarcted area through their controlled release properties. In the field of electrical conduction, hydrogels are used as scaffolding materials that mimic the mechanical and electrical properties of myocardial tissues. The role of hydrogels in immunomodulation has also attracted much attention. In addition, the application of hydrogels in biosensing and detection functions provides new strategies for real-time monitoring of MI. In summary, hydrogels have demonstrated multifunctional advantages in MI therapy, but their clinical applications still face challenges, such as the long-term biocompatibility of the materials and the feasibility of large-scale production. Future research should focus on optimizing the design of hydrogels for more precise treatment and wider applications.

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1 Introduction

Myocardial Infarction (MI) is a serious heart condition caused by reduced or complete interruption of blood flow to a portion of the heart muscle.[1–3] This condition can lead to death and necrosis of heart muscle cells, which can lead to heart dysfunction.[4,5] Most myocardial infarctions are caused by atherosclerosis of the coronary arteries.[6,7] Patients with myocardial infarction may present with discomfort or pressure in the chest, which may radiate to the neck, jaw, shoulders, or arms.[8,9] In addition to history and physical examination, myocardial ischemia may be accompanied by electrocardiographic changes and elevated biochemical markers, such as cardiac troponin.[9,10] The first case finding of myocardial infarction dates back to 1768, when William Heberden, an English physician, first applied the term angina pectoris (angina) and described the symptoms associated with myocardial infarction.[11,12] The description of myocardial infarction in 1773 by another English physician, John Hunter, marked the beginning of the understanding of myocardial infarction.[13–15] Treatments for myocardial infarction have advanced since its discovery, but the mortality rate for acute myocardial infarction remains 5–30%, with the majority of deaths occurring before arrival at the hospital.[16] In addition, within one year after myocardial infarction, there is an additional mortality rate of 5% to 12%, and the overall prognosis depends on the extent of myocardial injury and left ventricular ejection fraction.[17–19] Therefore, treatment of myocardial infarction and improvement of prognosis are particularly important. Treatment of myocardial infarction mainly consists of pharmacologic therapy, reperfusion therapy, or heart transplantation, which exist to improve myocardial infarction to some extent, but all of these methods have limitations.[20,21]

Drugs used in the pharmacologic treatment of myocardial infarction include antiplatelet agents, anticoagulants, nitrates, beta blockers, statins, angiotensin receptor blockers, and vascular converting enzyme inhibitors.[22,23] Table 1 lists the advantages, disadvantages of these drugs in MI. Reperfusion therapy for myocardial infarction includes thrombolytic drugs, percutaneous coronary intervention and coronary artery bypass grafting. Thrombolytic drugs include urokinase, streptokinase, aniprase, tissue-type fibrinogen activator, and glucokinase.[24–26] Table 2 lists the advantages, disadvantages of these drugs in MI. The thrombolytic mechanism of all these drugs requires activation of fibrinolytic enzymes, and their main action is to

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Table 1 Classification of drugs involved in the pharmacologic approach to MI and their advantages and disadvantages

Type of drugs	Representative drugs	Advantages	Disadvantages	References
Antiplatelet drug	Acetylsalicylic acid, clopidogrel, dipyridamole, abciximab, *et al.*	Prevents thrombosis and reduces the size of myocardial infarction, improves blood flow to the heart	Gastrointestinal bleeding, cerebral hemorrhage, *et al.*	22 and 23
Anticoagulant	Warfarin, heparin, low molecular weight heparins (enoxaparin, dalteparin, tinzaparin)	Prevents blood clotting and reduces thrombosis	Visceral bleeding, skin petechiae, *et al.*	22 and 23
Nitrate drugs	Glyceryl trinitrate, isosorbide dinitrate, isosorbide mononitrate, pentaerythritol tetranitrate, *et al.*	Reduces heart load and relieves angina	Headache, low blood pressure, dizziness, *et al.*	22 and 23
β-blocker	Propranolol, metoprolol, bisoprolol, atenolol, carvedilol, arotinolol, labetalol, *et al.*	Reduces heart rate and blood pressure, reduces myocardial oxygen consumption	Fatigue, dyspnea, bradycardia, *et al.*	22 and 23
Statins	Atorvastatin, rosuvastatin, lovastatin, simvastatin, pravastatin, fluvastatin, pitavastatin, *et al.*	Lower cholesterol and stabilize plaque	Muscle pain, abnormal liver function, rhabdomyolysis, *et al.*	22 and 23
Angiotensin receptor blockers	Losartan, valsartan, irbesartan, olmesartan, telmisartan, *et al.*	Reduced cardiac load, improved cardiac remodeling, reduced heart failure	Dizziness, headache, fatigue, nausea and vomiting, *et al.*	22 and 23
Angiotensin-converting enzyme inhibitors	Captopril, enalapril, benazepril, lisinopril, ramipril, fosinopril	Reduced cardiac load, improved cardiac remodeling, reduced heart failure	Dry cough, hypotension, renal function deterioration, hyperkalemia, *et al.*	22 and 23

dissolve blood clots in the coronary arteries, restore blood flow, and reduce myocardial damage and infarct size, thereby improving the symptoms of myocardial infarction.[24–26] However, since their thrombolytic action is non-selective, this increases the risk of bleeding. For this reason, when using these medications, physicians weigh the patient's risk of bleeding against the potential benefit of myocardial infarction to determine the most appropriate treatment option. Percutaneous Coronary Intervention (PCI) and Coronary Artery Bypass Grafting (CABG) for atherosclerosis are two commonly used treatments, both of which improve long-term survival.[27–29] PCI is a minimally invasive procedure that requires less time, is less invasive, and has

Table 2 Classification of reperfusion therapies for MI and their advantages and disadvantages

Drugs	Advantages	Disadvantages	References
Urokinase (UK)	An endogenous fibrinolytic enzyme; promotes fibrinolysis; relatively inexpensive; non-pyrogenic and non-antigenic	Causes allergic rashes; relatively low rate of revascularization; prone to systemic fibrinolytic state, increasing the risk of hemorrhage	24–26
Streptokinase (SK)	Remarkable thrombolytic effect; promoting the conversion of free fibrinogen to fibrinolytic enzymes for fibrinolysis	Poor specificity, prone to a range of adverse effects including allergic reactions and hypotension	24–26
Aniplase (APSAC)	Antigen-free glycoprotein; strong local thrombolytic effect, non-antigenic, mild depletion of fibrinogen	Short half-life, requires continuous intravenous administration, relatively expensive	24–26
Tissue-type fibrinogen activator (t-PA)	Specific affinity, selective activation of fibrinogen in blood clots, strong local thrombolytic effect	Short half-life, requires continuous IV administration, more expensive	24–26
Glucokinase (r-SAK)	Fibrinogen activator derived from marine organisms with thrombolytic effect	Can cause adverse effects; not as commonly used as other thrombolytic drugs	24–26

a faster recovery than open-heart surgery, and it is suitable for a wide range of coronary artery lesions, especially for patients with single- or double-vessel lesions.[29,30] However, there may be a risk of restenosis after PCI and it is not as effective as CABG for multivessel lesions or left main lesions.[31] CAGB offers better long-term survival and symptomatic relief for multibranch vascular lesions or left main lesions, significantly improving patients' long-term survival while reducing the risk of rejection.[32] However, CABG is an open-heart procedure that is more invasive and has a longer postoperative recovery time. Heart transplantation is an effective treatment for end-stage heart disease, and the severe shortage of donor organs is one of the great challenges to heart transplantation, with post-transplantation complications and rejection limiting the procedure.

Therefore, it has become particularly important to develop new therapeutic strategies to improve cardiac function after myocardial infarction and prevent the development of heart failure. Hydrogels, as a new type of biomaterial, played an important role in many fields of biology. For example, lubricating hydrogels provided a new approach to the treatment of cartilage diseases.[33,34] A study reported that by designing hydrogels that separated mechanical robustness from lubrication sustainability, the challenge of mutual dependence between mechanical degradation and accelerated lubrication failure in traditional designs was overcome, thereby enabling hydrogels to perform load-bearing lubrication at the cartilage interface.[35] In addition, hydrogel shows great potential in the treatment of myocardial infarction.[36,37] Hydrogels can facilitate cardiac repair after myocardial infarction through several mechanisms. First, hydrogels can be used as carriers for drugs, growth factors or cells for targeted delivery and controlled release.[38] Second, the three-dimensional network structure of hydrogels can mimic the extracellular matrix, providing a favorable growth environment for cardiomyocytes.[39] In addition, hydrogels can reduce ventricular remodeling and improve cardiac function through physical filling effects. Researchers have developed several types of hydrogels, including natural hydrogels (*e.g.*, gelatin, hyaluronic acid) and synthetic hydrogels (*e.g.*, polylactic acid-hydroxyacetic acid copolymer).[40,41] These hydrogels can be designed to have different physical and chemical properties to suit different therapeutic needs. For example, some hydrogels have excellent biocompatibility and biodegradability, while others have electrical conductivity or self-healing capabilities.[42,43] Although hydrogels have shown promising results in the treatment of myocardial infarction, their clinical application still faces a number of challenges. These challenges include the long-term stability of hydrogels, their biosafety, and how to optimize the injection and implantation methods of hydrogels. Future research needs to address these issues to realize the widespread use of hydrogels in myocardial infarction therapy. With advances in materials science and biotechnology, hydrogel research and applications will continue to evolve. In the future, hydrogels may integrate more bioactive factors, such as stem cells, exosomes, or gene therapeutic agents, for more effective cardiac repair and regeneration.[44,45] In addition, the development of smart-responsive hydrogels will allow dynamic adjustment of drug release in response to changes in the cardiac microenvironment, further improving therapeutic efficacy.[46–48] The article summarizes recent research advances based on the role of hydrogel materials in myocardial infarction, laying the groundwork for the application and expansion of hydrogel materials in myocardial infarction (Fig. 1). It concludes with a summary of the challenges facing the field and a look at emerging new directions.

2 Function of hydrogels in myocardial infarction

The use of hydrogel materials in the treatment of myocardial infarction was an active area of research, with the main advantage being the ability to provide a minimally invasive treatment by delivering the material directly to the damaged myocardial tissue by means of injection. The main functions performed by hydrogels during myocardial infarction include drug delivery function,[49] electrical signaling function,[50,51] detection function, stem cell delivery function,[52] immunomodulatory function[53,54] and detection function. Hydrogels were used as carriers for delivering drugs to improve cardiac function by delivering anti-inflammatory drugs or growth factors and controlling the release of the drugs, reducing inflammatory response and fibrosis, increasing therapeutic efficacy and reducing side effects.[55] Some hydrogels were designed to be electrically conductive to improve electrical signaling in damaged heart muscle and reduce the risk of arrhythmia.[56] In addition, some hydrogels were able to detect myocardial infarction recovery while performing therapeutic functions. In addition, some hydrogels incorporated microfluidic systems to perform tissue engineering functions. Therefore, the aim of this review is to describe the role played by hydrogels in myocardial infarction and their prospects for clinical applications.

2.1 Hydrogel with drug delivery function

Hydrogels, as biocompatible polymeric materials, could precisely deliver drugs to the infarct area through injection or implantation, achieving local sustained release, improving efficacy, and reducing side effects.[57,58] The three-dimensional network structure of hydrogels loaded various drugs, including anti-inflammatory drugs,[59] antioxidants,[60] growth factors,[61] cell chemokines[62] and miRNA.[63] These substances played an important role in the treatment of myocardial infarction. For example, anti-inflammatory agents,[59] growth factors, and cell chemokines[62,64,65] promoted myocardial repair and vascular regeneration. The adjustable mechanical properties and degradation rate of hydrogels enabled them to adapt to the dynamic environment of the heart and provided sustained drug release.[66] In addition, hydrogels achieved smart controlled release by responding to stimuli such as temperature, pH, or enzymes, further enhancing therapeutic efficacy.[67] In the future, hydrogels will be more widely used in the treatment of myocardial infarction. Combined with nanotechnology and gene therapy, they are expected to bring breakthrough progress

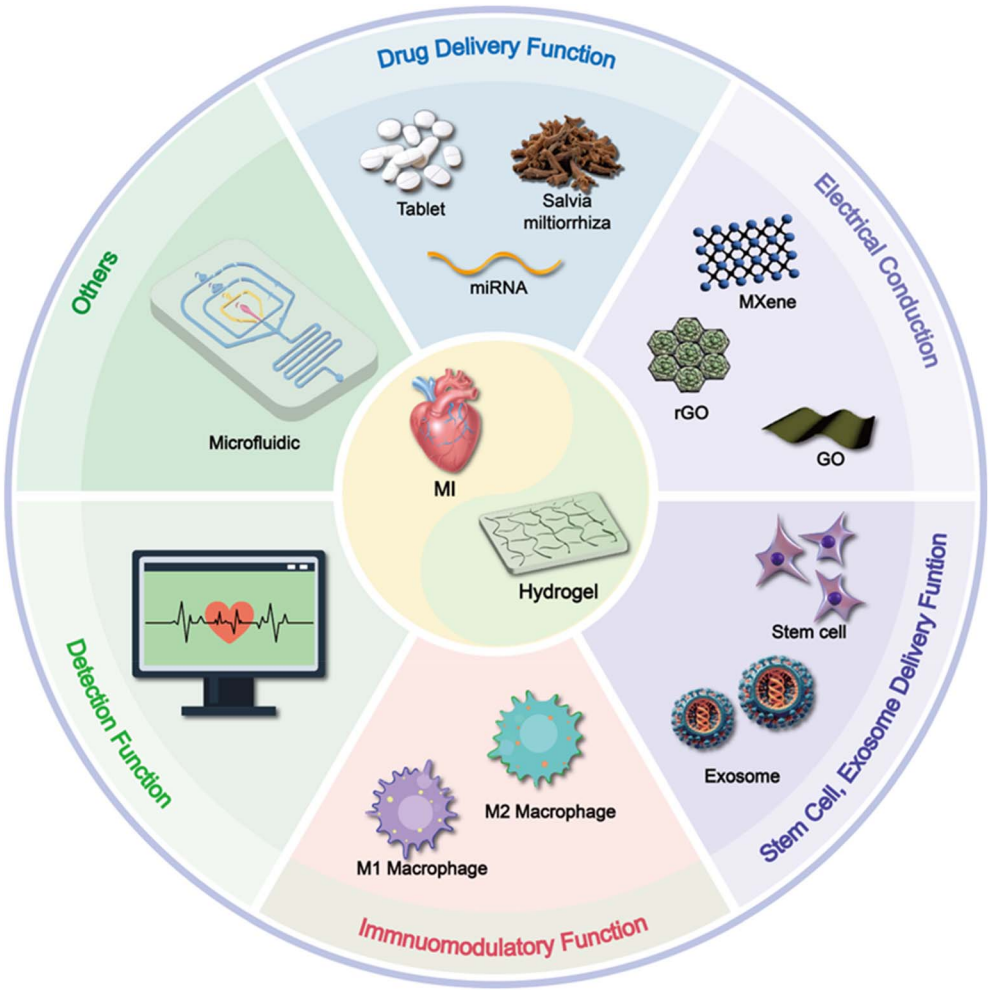

Fig. 1 Schematic representation of hydrogels functioning in myocardial infarction.

in the treatment of cardiovascular diseases. Therefore, this section will discuss hydrogel delivery of chemokines, growth factors, miRNAs, antioxidants, and anti-inflammatory drugs in that order. In addition, Table 3 showed a comparison of the advantages and disadvantages of the five hydrogels in terms of drug delivery.

SDF-1α (stromal-derived factor 1α), as a chemokine CXCL12 (chemokine receptor 4), has been shown to promote cardiac repair. A hydrogel loaded with SDF-1α formed into a network structure by puerarin (PUE) played an important role in myocardial infarction. This hydrogel was cross-linked into a three-dimensional network of flowable, injectable hydrogel

Table 3 Comparison of 5 types of hydrogels in terms of drug loading and delivery

Hydrogel type	Drug loading advantage	Drug release advantages	Main limitations	References
SDF-1α@PUE hydrogel	Electrostatic adsorption of high loads	Passive sustained release, protecting drug activity	Lack of environmental responsiveness	68
GST-TIMP-bFGF/Gel-GSH hydrogel	GST-GSH specific binding	MMPs trigger on-demand release	Dependent on MMP expression levels	69
CD-AD/HA/miR-302 hydrogel	Dynamic self-assembly, compatible with nucleic acid drugs	Shear response injection	Weak macromolecular loading capacity	70
FPDA/α-TOH hydrogel	Multifunctional (conductive + antioxidant)	ROS microenvironment regulation	Complex synthesis, limited types of drugs that can be loaded	71
ECM-NCL hydrogel	Natural ECM support, long-lasting slow release of NCLs	Anti-inflammatory and fibrosis inhibition	High viscosity may affect release uniformity	55

through the superimposition of PUE intermolecular benzene rings, hydrogen bonds, and hydrophobic interactions. Positively charged SDF-1α and negatively charged PUE were loaded into the three-dimensional network hydrogel through electrostatic adsorption, which improved drug loading capacity. The rheological properties and release characteristics of SDF-1α@PUE ensured the successful delivery of SDF-1α to the site of myocardial focal damage, while also enabling the effective release of SDF-1α. SDF-1α@PUE hydrogel promoted angiogenesis by promoting the polarization of MI macrophages into M2-type macrophages, increased Cx43 (connexin 43) expression in heart tissue after myocardial infarction, and had a strong anti-inflammatory effect, thereby significantly promoting the repair process of myocardial infarction and heart tissue (Fig. 2A).[68] This injectable drug-loaded hydrogel provides a new direction for the treatment of myocardial infarction and the repair of cardiac tissue.

Growth factors had strong angiogenesis capabilities. Therefore, they were widely used in the treatment of myocardial infarction. Basic fibroblast growth factor (bFGF), one of the most effective growth factors, was fused with glutathione-S-transferase (GST) and the peptide segment PLGLAG (TIMP) that could be cleaved by MMP-2/9 (Matrix Metalloproteinase-2/9) to produce the GST-TIMP-bFGF recombinant protein.[69] The GST in this protein specifically bound to GSH in the GSH-modified collagen hydrogel (Gel-GSH) formed by cross-linking between the amino acids of collagen and the sulfhydryl groups of glutathione (GSH), resulting in a high-load GST-TIMP-bFGF Gel-GSH hydrogel. The cross-linking of collagen amino groups and GSH thiol groups formed hydrogel that ensured its rheological properties at room temperature. This feature allowed the hydrogel to be specifically injected into the myocardial infarction lesion site. TIMP peptides, as cleavable sequences of MMP-2/9, responded to the overexpression of MMPs in the infarction area to achieve on-demand release of bFGF. Gel-GSH hydrogels loaded with GST-TIMP-bFGF inhibited the expression of MMPs after myocardial infarction and reduced the degradation of myocardial ECM. In addition, the on-demand release of bFGF promoted angiogenesis by inhibiting MMPs and effectively slowed down the development of cardiac remodeling by altering collagen subtypes (Fig. 2B).[69] In summary, the combined delivery system of Gel-GSH hydrogel and GST-TIMP-bFGF provided a multifunctional and responsived strategy for the treatment of myocardial infarction. Through precise drug release, matrix protection, and promotion of angiogenesis, it offered new research directions and application prospects for myocardial repair and functional recovery.

Hyaluronic acid was modified with β-cyclodextrin (CD) and adamantane (AD) respectively. The high affinity of CD and AD enabled the formation of hydrogels when mixed. This self-assembled hydrogel had shear-thinning and self-healing properties. These unique rheological characteristics enabled it to liquefy under shear stress during injection and rapidly returned to a gel state once the shear stress was removed, thereby achieving precise delivery to cardiac tissue. A miR-302 analog modified at one end binds to cholesterol through the interaction between cholesterol and CD, enabling the hydrogel to load miR-302. Cholesterol modification of miR-302 mimics enhanced cellular uptake of miR-302 while improving the affinity of the hydrogel. After injection of the miRNA-loaded composite hydrogel into the myocardial infarction area, miR-302 was continuously released and temporarily activated the cardiac cell cycle, thereby promoting cardiac regeneration and achieving cell proliferation and functional improvement (Fig. 2C).[70] In addition, this miRNA-based hydrogel delivery system provided an efficient and controllable strategy for mammalian heart regeneration, overcoming the limitations of traditional methods in terms of drug release and targeting.

α-Tocopherol (α-TOH) was the most potent antioxidant and could significantly reduce the incidence of cardiovascular disease. The synthesis of FPDA (F127DA-PEDOT: PSS-PDA-α-TOH) hydrogel was completed in two steps. First, F127DA (Pluronic F127 diacrylate) molecules in the aqueous solution self-assembled into micelles through hydrophobic interactions of the PPO segments. The hydrophobic core region of the micelles encapsulated α-TOH, resulting in a hydrogel solution. DA (dopamine) reacted with the catechol and quinone groups on the F127DA molecule to form PDA (polydopamine) chains. Finally, conductive PEDOT: PSS (poly (3,4-ethylenedioxythiophene): poly (styrenesulfonate)) was added, and under the presence of a photoinitiator, photopolymerization occurred, thereby forming a composite FPDA hydrogel with high conformability, antioxidant properties, and conductivity. Both covalent and non-covalent interactions (such as electrostatic interactions, hydrogen bonds, hydrophobic interactions, π–π stacking, *etc.*) participated in the cross-linking process to form a hydrogel network (Fig. 2D).[71] The high compliance of the composite hydrogel ensured that it could be injected into the infarction area. α-TOH endowed the hydrogel with antioxidant properties. This characteristic enabled the hydrogel to clear ROS (reactive oxygen species) in the myocardial infarction area, reduced myocardial fibrosis, upregulated the expression of α-SMA (α-Smooth Muscle Actin) and CD31 (platelet endothelial cell adhesion molecule 1), and promoted myocardial tissue regeneration. In addition, the conductivity of FPDA hydrogel effectively simulated the conductive microenvironment of natural cardiac tissue, contributing to the promotion of normal cardiac electrical conduction (Fig. 2D).[71] In summary, FPDA hydrogel, as a multifunctional injectable material, not only possessed excellent mechanical properties and biocompatibility, but also actively regulated the microenvironment after myocardial infarction by releasing drugs, which significantly improved the therapeutic effect. This study provided new ideas and experimental basis for the treatment of myocardial infarction, and further promoted the application of drug-carrying hydrogels in the field of cardiovascular repair.

Extracellular matrix (ECM) hydrogels were formed by hydrogen bonds, electrostatic interactions, van der Waals forces, and hydrophobic interactions between fibrin molecules. NCLs (nanostructured lipid carriers) containing colchicine had strong adhesive properties. Adding NCLs to the ECM hydrogel precursor solution caused the NCLs to adhere to the fibrin surface, forming an ECM-NCL hydrogel. The fluidity and network structure of ECM-NCL hydrogels ensured that small

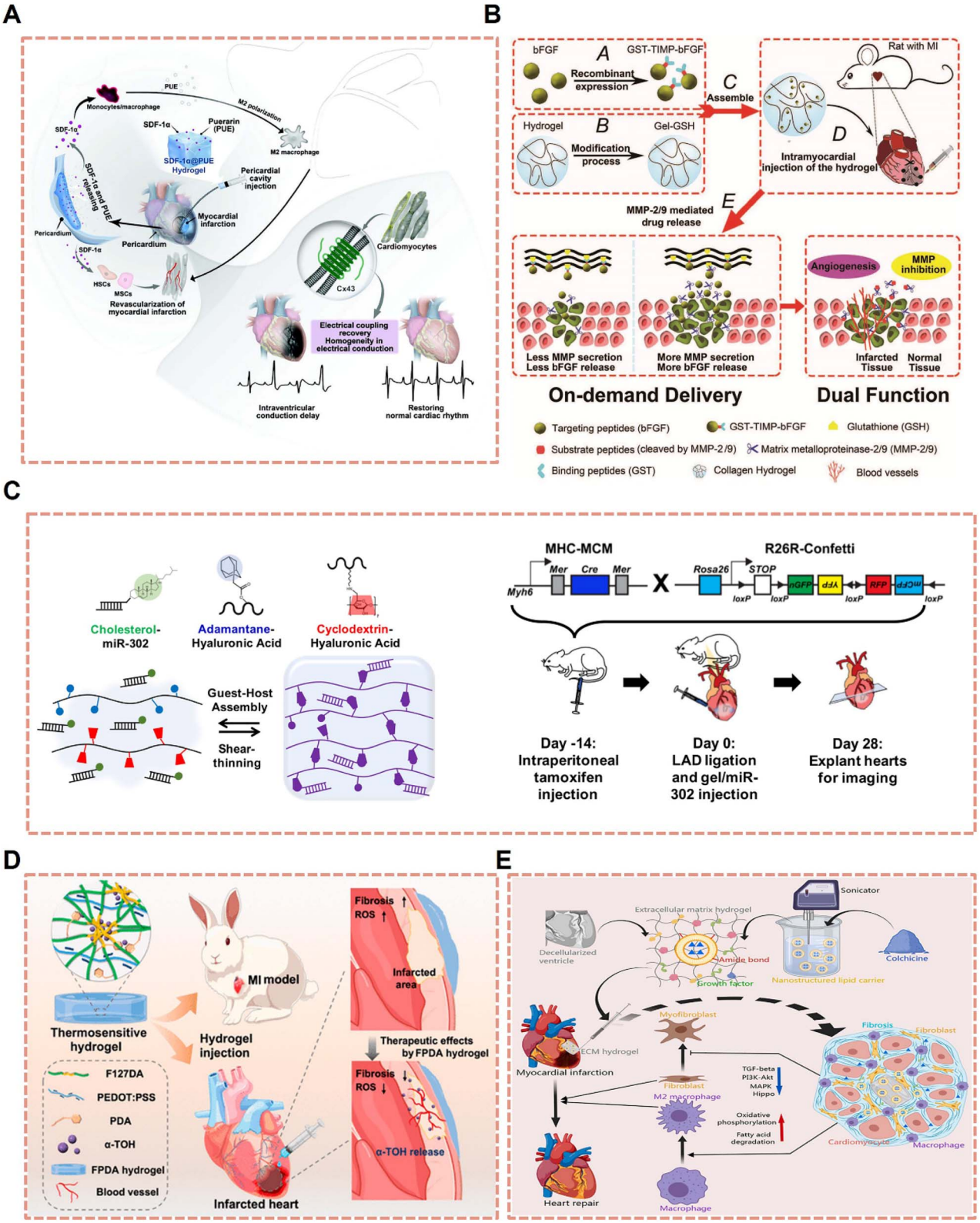

Fig. 2 Hydrogels that perform drug delivery functions in MI. (A) Flow diagram of the role of hydrogel-loaded SDF-1a in MI.[68] (B) Drug release process of hydrogels efficiently loaded with GST-TIMP-bFGF and its mechanism of action in the treatment of MI are mapped.[69] (C) Schematic illustration of injectable hydrogel control release of cholesterol-miR-302 mimics to promote myocardial regeneration in MI.[70] (D) Principle of slow release of tocopherol from hydrogels to reduce infarct size and increase ejection fraction.[71] (E) Schematic representation of colchicine-loaded hydrogel for repair of MI by localized efficient release of colchicine.[55]

molecule drugs could be delivered locally and continuously to the myocardium. Colchicine released from ECM-NCL hydrogels participates in cardiac repair after myocardial infarction through anti-inflammatory effects and downregulation of Wnt, Hippo, and Transforming growth factor-β (TGF-β)-related signaling pathways. The ECM-NCL hydrogel treatment group showed significant improvement in cardiac function, as evidenced by increases in key indicators such as cardiac output and ejection fraction. Additionally, the ECM-NCL hydrogel significantly increased vascular density in the infarct area and markedly reduced fibrosis, further confirming that this hydrogel system had a dual effect of promoting angiogenesis and inhibiting fibrosis (Fig. 2E).[55] In summary, ECM-NLC hydrogel combined the sustained-release advantages of a nanocarrier system with the biological activity of decellularized ECM, providing an effective therapeutic strategy for cardiac repair after myocardial infarction. Future research may further optimize drug release kinetics and explore its long-term efficacy and molecular mechanisms to advance its clinical translation and application.

2.2 Hydrogel with electrical conduction function

In the therapeutic field of myocardial infarction, hydrogels have received attention not only for their precision in drug delivery, but also for their potential in restoring the electrical conduction function of the heart. Scar tissue after myocardial infarction disrupted the normal electrical conduction of the heart, leading to arrhythmias.[72,73] Hydrogels, especially those composites with conductive properties, could be used as bioelectronic interfaces to be implanted into damaged regions of the myocardium to restore the transmission of electrical signals.[56,74] These conductive hydrogels were usually made of conductive nanomaterials (*e.g.*, MXene, graphene) combined with biocompatible polymers, which maintained the flexibility and biocompatibility of the hydrogel while imparting good electrical conductivity.[75] They were able to form a tight electrical coupling with cardiomyocytes and promote the synchronized propagation of electrical signals, thereby improving the contraction coordination of the heart.[76,77] For example, conductive hydrogels enhanced the electrical coupling ability of cardiomyocytes by improving electrical signal conduction, thereby promoting the recovery of cardiac function.[78,79] In addition, conductive hydrogels could be used in combination with pacemakers or defibrillators to provide additional electrical stimulation support to the heart, further optimizing the therapeutic effect.[80] With advances in materials science and biomedical engineering, the application of conductive hydrogels in the treatment of myocardial infarction is promising and is expected to bring new hope to heart patients. In addition, Table 4 showed a comparison of the advantages and disadvantages of four types of conductive hydrogels in MI repair.

Conductive hydrogel-based cardiac patch technology has received much attention in the field of cardiac repair after MI. These materials not only provided mechanical support to the damaged myocardium, but also promoted functional recovery of the electroactive tissue through electrical conduction properties. A study used chemical cross-linking and physical interactions between two-dimensional titanium carbide ($Ti_3C_2T_x$ MXene), gelatin, and dextran-aldehyde to form a hydrogel (CAHs) with conductivity and tissue adhesion properties. The amino group (–NH_2) of gelatin reacted chemically with the aldehyde group (–CHO) of dextran to form dynamic covalent bonds, achieving rapid gelation (approximately 250 seconds). This crosslinking conferred injectability and spreadability to the hydrogel, facilitating *in situ* molding on the heart surface. The hydrophilic groups on the surface of MXene nanosheets, such as –OH, –O, and –F, interacted with the gelatin/dex-ald network through hydrogen bonds, enhancing mechanical properties. The uniform dispersion of MXene prevented the aggregation of gelatin and dextran, forming conductive pathways (conductivity of 18.3 mS cm^{-1}). The aldehyde groups of dextran reacted with the amino groups on the surface of cardiac tissue to form Schiff base bonds, while the polar groups of gelatins (such as carboxyl and hydroxyl groups) bound to the tissue *via* hydrogen bonds and electrostatic interactions, thereby enhancing the adhesion of CHAs to cardiac tissue. Gelatin/dex-ald improved the biocompatibility of CHAs, and MXene formed the electrical conduction network of CHAs. The high conductivity of CHAs hydrogels formed an "electrical bypass" in the myocardial infarction area, thereby restoring point coupling between myocardial cells and promoting synchronized contraction of the heart. Simultaneously,

Table 4 Comparison of the advantages and disadvantages of four types of conductive hydrogels in MI repair

Hydrogel type	Conductivity advantages	Main drawbacks	Applicable scenarios	References
MXene/CHAs hydrogel	High conductivity (18.3 m S cm^{-1}), strong adhesion	MXene was easily oxidized, and its long-term stability needed to be optimized	Immediate repair during acute myocardial infarction surgery	78
CPAMC/PCA hydrogel	Dual functionality (conductive + anti-adhesion), ROS response	Conductivity not quantified, complex synthesis	Long-term implantable repair with anti-adhesion properties	81
PAM/BIS-CUR@PDA NPs hydrogel	Electromechanical sensing, anti-inflammatory	Ion conductivity was affected by the environment	Synchronized heart function monitoring and repair	82
GelMA-O5/rGo hydrogel	Stem cell synergy, high mechanical strength	Uneven distribution of rGO, potential risk of UV polymerization	Combined treatment with stem cell delivery and electroconvulsive therapy	83

enhanced electrical signal conduction increased the expression of connexin 43 (Cx43), improving the transmission of electrical signals between myocardial cells (Fig. 3A).[78] Additionally, the elasticity of the hydrogel provided mechanical support and resists myocardial remodeling. In summary, in myocardial infarction repair, CHAs hydrogels significantly improved cardiac function and inhibited fibrosis through electromechanical coupling and regulation of the cardiac microenvironment.

CPAMC/PCA Janus hydrogel was formed by multiple interactions between the CPAMC bottom layer hydrogel and the PCA top layer hydrogel, including adhesion, electrostatic adsorption, dynamic cross-linking, and permanent cross-linking. This hydrogel was characterized by double-sided asymmetric adhesion. The core component of the hydrogel was the underlying CPAMC hydrogel. It was composed of acrylic acid (AA), polyethyleneimine (PEI), aldehyde-functionalized cellulose (CNC-CHO), and *N*,*N*′-bis(acryloyl)cysteine (BAC) as dynamic crosslinking agents, potassium 3-sulfonic acid propyl methacrylate (MASEP), and caffeic acid (CA) containing catechol groups. The redox-responsive PAA/PEI/CNC-CHO/CA interpenetrating network structure was formed by the following interactions: hydrogen bonded between the carboxyl groups (–COOH) of acrylic acid and the amino groups (–NH_2) of polyethyleneimine (PEI), the formation of reversible Schiff bases between the aldehyde groups of CNC-CHO and the amino groups of PEI, ionic interactions between the negatively charged sulfonate groups in MASEP and the positively charged PEI, and interactions between the benzene rings of CA and the amino groups of PEI. PCA hydrogel, as the top layer of Janus hydrogel, was synthesized by AA, carboxylate cellulose (CNC-COOH), and anti-cell adhesion polyethylene glycol diacrylate (PEGDA) as crosslinking agents. AA and PEGDA formed a covalently crosslinked network with anti-cell adhesion and non-toxic properties under the action of an initiator (APS) and a catalyst (TEMED). MASEP and ionic networks provided conductive pathways, promoting electrical signal conduction and synchronized contraction of cardiomyocytes (CMs), thereby repairing electrical conduction disorders following myocardial infarction. CA and BAC responded to ROS enriched in ischemic regions, effectively clearing ROS in the infarct area and reducing oxidative damage. The catechol structure contained in CA enhanced the adhesion capacity of the hydrogel to cardiac tissue through covalent and non-covalent interactions. The polyethylene glycol (PEGDA) and carboxylate cellulose (CNC-COOH) in the top layer PCA hydrogel reduced macrophage aggregation and fibrosis, preventing postoperative adhesion between the heart and surrounding tissues (Fig. 3B).[81] In addition, CPAMC hydrogel promoted the transformation of MI-type macrophages into M2-type macrophages by suppressing the expression of iNOS (inducible nitric oxide synthase) and upregulating the expression of TGF-β (transforming growth factor beta) (Fig. 3B).[81] In summary, this hydrogel integrated adhesion, conductivity, antioxidant, anti-inflammatory, and anti-adhesion properties through multi-mechanism cross-linking and functional design, achieving the dual goals of non-invasive myocardial repair and postoperative adhesion prevention. In the future, further research based on CPAMC/PCA hydrogels is expected to promote their clinical application and open up new avenues for the treatment of cardiovascular diseases.

Conductive hydrogels based on nanocomposite enhancement technology showed remarkable potential in the field of MI repair and real-time monitoring. A study presented a strategy for synthesizing curcumin nanocomposite-enhanced ion-conductive hydrogels based on core–shell structures, aiming at simultaneous cardiac electrophysiological signal monitoring and infarcted heart repair (Fig. 3C).[82] The hydrogel was composed of ammonium persulfate, acrylamide (AM) monomer, double-layer core–shell structure curcumin@polydopamine nanoparticles (CUR@PDA NPs), and *N*,*N*′-methylenebisacrylamide (BIS). CUR@PDA NPs and BIS reacted to form BIS-CUR@PDA NPs. AM monomers and BIS-CUR@PDA NPs formed PAM/BIS-CUR@PDA NPs (PCP2) hydrogels through radical polymerization in the presence of persulfamide. BIS-CUR@PDA NPs acted as multifunctional chemical crosslinking points, connecting with AM chains through covalent bonds while enhancing network stability through noncovalent interactions such as hydrogen bonds. This crosslinking mechanism endowed the hydrogel with excellent mechanical properties and elasticity. Protons in the hydrogel provided ionic conductivity, with a conductivity matching that of natural cardiac muscle tissue (10^{-4}–10 S cm^{-1}). The conductivity of the hydrogel converted mechanical deformation into electrical signals, which were used for real-time monitoring of cardiac movement. The conductive microenvironment of the hydrogel promoted vascular endothelial cell migration and increased the density of new blood vessels in the infarct area. The release of curcumin from the hydrogel inhibited inflammatory responses by regulating macrophage polarization (from pro-inflammatory M1 type to reparative M2 type). In addition, the elastic modulus of the hydrogel was similar to that of myocardial tissue, providing mechanical support and inhibiting ventricular dilatation (Fig. 3C).[82] In summary, this conductive hydrogel cardiac patch provided a multifunctional strategy for myocardial infarction repair by integrating bioactivity, electrophysiological sensing, and mechanical support functions. Future studies could further optimize its sensing performance and biocompatibility and explore its potential application in other electroactive tissue repair to facilitate its clinical translation.

A novel injectable conductive hydrogel based on graphene oxide and GelMA/ODEX (gelatin methacrylate/oxidized dextran) showed significant application potential in the treatment of MI. The aldehyde groups of oxidized dextran (ODEX) reacted with the amino groups of gelatin methacrylate (GelMA) to form dynamic covalent bonds (imine bonds), constituting a primary cross-linked network structure. Under the action of the initiator (LAP) and ultraviolet light, the methacrylate groups in GelMA underwent free radical polymerization to form a stable covalent cross-linked network structure. Subsequently, rGO obtained by reducing graphene oxide (GO) with dopamine under weakly alkaline conditions was physically doped into the cross-linked network hydrogel to obtain GelMA-O5/rGO hydrogel. Finally, umbilical cord mesenchymal stem cells (UCMSCs) were encapsulated in GelMA-o5/rGO hydrogel. The dual crosslinking

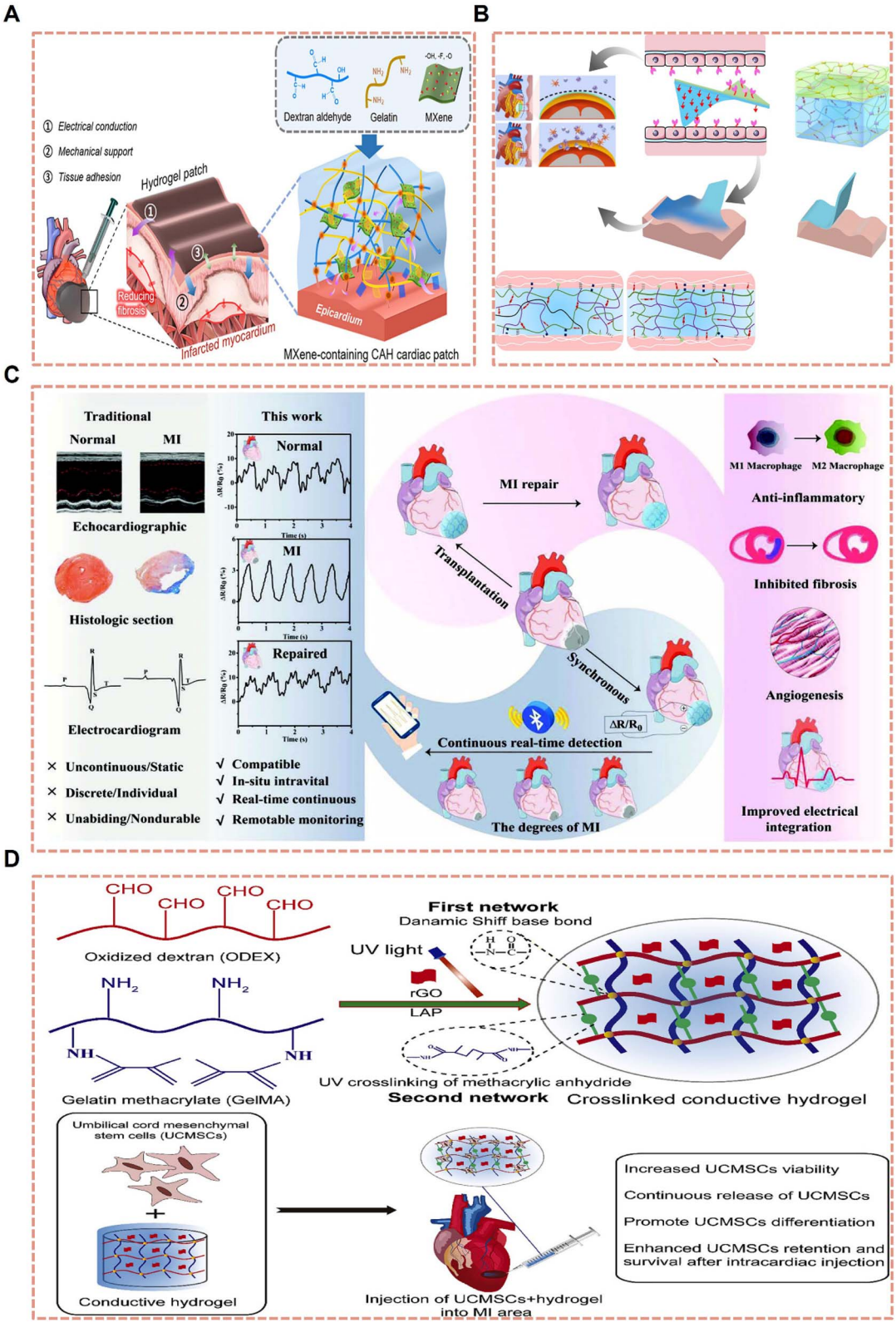

Fig. 3 Hydrogel with electrical conduction function. (A) Schematic drawing of high conductivity CAH formed by MXene, gelatin and dextran aldehyde to improve cardiac function.[78]. (B) Flow chart of CPAMC/PCA hydrogel providing mechanical-electrical coupling function and reactive oxygen species (ROS) scavenging ability for MI repair.[81] (C) Mechanism of curcuma longa's enhancement of hydrogel electrical conductivity and its function in MI.[82] (D) Schematic diagram of the role of GelMA-O5/rGO hydrogel in myocardial infarction.[83]

of GelMA-ODEX significantly increased the compressive modulus of the hydrogel, enabling it to withstand the cyclic stress of cardiac contractions. The addition of rGO increased the conductivity of the hydrogel to 2.36×10^{-4} S cm^{-1}, which matched that of myocardial tissue (5×10^{-5}–1×10^{-3} S cm^{-1}), thereby promoting myocardial electrical signal conduction and coordinating synchronous contraction of myocardial cells. After encapsulating UCMSCs in hydrogel, they were injected into the myocardial infarction area. The conductivity activated the differentiation of UCMSCs into cardiomyocytes, and upregulated the expression of cardiac markers (cTnI) and Cx43, thereby improving myocardial electrical signal conduction. Improved conduction of myocardial electrical signals increased cardiac ejection fraction (EF) and shorted fraction (FS) and inhibited ventricular remodeling. In addition, the porous structure of the hydrogel promoted nutrient exchange between UCMSCs and the external environment, improving cell survival rates (Fig. 3D).[83] This study provided an innovative strategy for the treatment of myocardial infarction and demonstrated the broad application prospects of the injectable conductive hydrogel system based on GelMA-O5/rGO in myocardial repair. In the future, this technology is expected to be further optimized and applied in clinical settings, providing new solutions for the treatment of cardiovascular diseases.

2.3 Hydrogel for delivery of stem cells, exosomes

Hydrogels showed great potential in myocardial infarction therapy, especially in stem cell and exosome delivery. Its three-dimensional network structure could mimic the extracellular matrix, providing a favorable growth environment for stem cells and promoting cell survival, proliferation and differentiation.[84,85] At the same time, hydrogels were used as a delivery carrier for exosomes, prolonging the retention time of exosomes in myocardial tissues and enhancing their repair effect through slow release.[86,87] Hydrogels had good biocompatibility and degradability, and were able to adjust the physicochemical properties, such as mechanical strength and degradation rate, according to the needs to adapt to different therapeutic needs.[88] In addition, hydrogels were modified by functionalization to further enhance their targeting and therapeutic effects.[89,90] Studies have shown that hydrogel-based stem cell and exosome delivery systems effectively improved cardiac function after myocardial infarction, reduce scar formation, and promote neovascularization, providing a new therapeutic strategy for myocardial repair.[91] In addition, Table 5 showed a comparison of the advantages and disadvantages of the three hydrogels in terms of encapsulating stem cells/exosomes.

In recent years, injectable hydrogels encapsulating stem cells or exosomes have shown significant potential in the field of anti-adhesion and myocardial protection after cardiac surgery. A study has developed an injectable hydrogel with asymmetric adhesion properties, composed of HAD (hyaluronic acid-g-(2-aminoethyl methacrylate hydrochloride-dopamine) hydrogel encapsulating iCM-EXOs (human induced pluripotent stem cells (hiPSC)-exosomes). HAD hydrogel was composed of hyaluronic acid (HA), dopamine hydrochloride (DA), 2-methylacrylamidoethyl methacrylate (AEMA), and a photoinitiator. Under 365 nm UV light irradiation, the C=C double bond of AEMA underwent free radical polymerization, forming a covalent cross-linked network structure. After cross-linking, the phenol groups of DAs were fixed in the network and restricted from free movement, thereby imparting asymmetric adhesiveness to the hydrogel. Uncross-linked DA groups bound to proteins (amino groups, thiol groups, *etc.*) on the surface of cardiac tissue, exhibiting strong adhesiveness. The strong adhesive properties of hydrogels sealed cardiac wounds and prevented blood and fibrin from seeping out. HAD precursor solutions had shear-thinning properties, which ensured that hydrogels could be precisely applied to cardiac wounds *via* injection. In addition, the negative surface charge of HA inhibited cell adhesion and reduces macrophage infiltration and fibrosis. The hydrogel released iCM-EXOs, which inhibited the Nrf2 (NF-E2-related factor-2) pathway (downregulating HO-1 (heme oxygenase-1) and NQO1 (quinone oxidoreductase 1)), reduced reactive oxygen species (ROS) production, and protected myocardial cell mitochondrial function (Fig. 4A).[92] In summary, hydrogels loaded with iCM-EXOs provided a multifunctional strategy for post-cardiac surgery treatment by integrating anti-adhesion, antioxidant, and extracellular vesicle delivery functions.

In recent years, intrapericardial injection has attracted widespread attention as a novel cellular or cell-derived exosome delivery strategy in the field of myocardial infarction therapy. A study reported the synthesis of a photopolymerizable MA-HA hydrogel by combining methacrylic acid (MA), hyaluronic acid (HA), and a photoinitiator. MA and HA underwent radical polymerization under UV light exposure, forming a covalent

Table 5 Comparison of the advantages and disadvantages of three types of hydrogels in encapsulating stem cells/exosomes

Hydrogel type	Core strengths	Main limitations	Applicable scenarios	References
HAD/iCM-EXOs hydrogel	Anti-adhesion, anti-oxidation, precise wound closure	UV toxicity, DA load balancing difficulty	Immediate repair and adhesion prevention after cardiac surgery	92
MA-HA/MSC-exohydrogel	Pericardial compatibility, minimally invasive delivery, sustained release	Uncontrollable release, insufficient mechanical strength	Repair of chronic MI by intrapericardial injection	62
GelMA/ECFCs-MSCs hydrogel	Natural ECM support, immune modulation, angiogenesis	Lack of environmental responsiveness, potential UV cell damage	Cell therapy and vascular reconstruction for acute MI	93

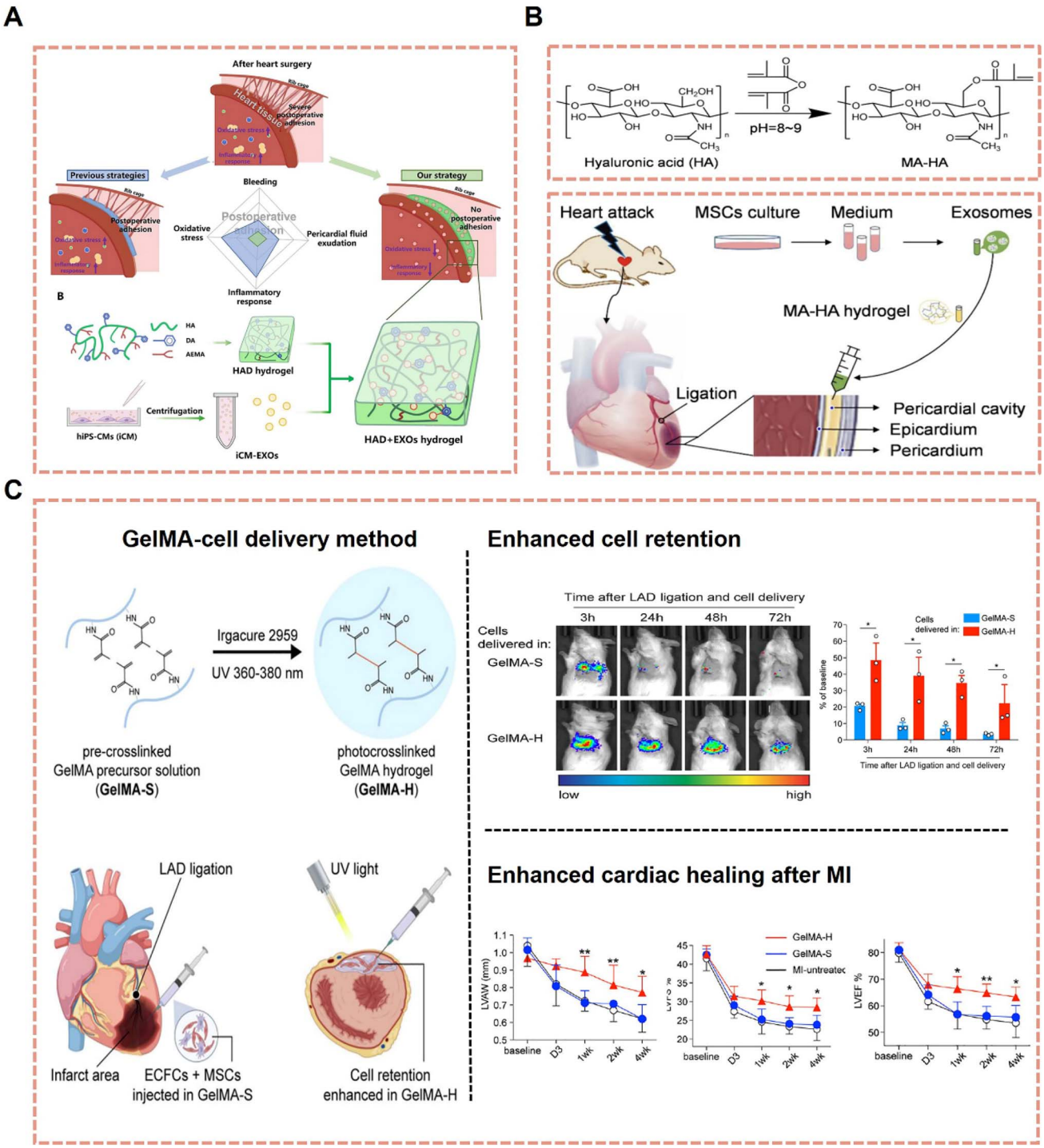

Fig. 4 Hydrogel for stem cell, exosome delivery function. (A) Flowchart of the continuous delivery of injectable Janus hydrogel to induce the function of pluripotent stem cell-derived cardiomyocyte exosomes (iCM-EXOs).[92] (B) Diagram of HA-MA-Exo for cardiac repair.[62] (C) The role of GelMA hydrogel encapsulated ECFCs and MSCs in myocardial infarction.[93]

crosslinked network structure. MA-HA hydrogels encapsulating mesenchymal stem cells (MSC) secreted exosomes (Exo) were used for pericardial injection after myocardial infarction. HA was the main component of pericardial fluid and had low immunogenicity. MA modification introduced controllable cross-linking sites. Hyaluronidase mediated the degradation of the hydrogel, and the degradation time could be regulated. In addition, the stiffness of the hydrogel could be adjusted by regulating the degree of MA substitution and the UV dose, enabling the hydrogel to adapt to the dynamic environment of the pericardial cavity. MA-HA hydrogel three-dimensional porous network structure loaded with exosomes gradually

released exosomes through diffusion and gel degradation, achieving the effect of long-term action of exosomes on myocardial tissue. The hydrogel physically isolated the pericardium from the thoracic cavity, reducing pericardial adhesion and inflammatory cell infiltration. Exo released from hydrogels was taken up by the pericardial outer membrane, promoting proliferation and differentiation by increasing Ki67 expression and progenitor cell numbers, thereby indirectly contributing to myocardial repair. Additionally, exosomes downregulated TGF-β expression while reducing collagen deposition to achieve an anti-fibrotic effect. These improvements enhanced the ejection fraction of the heart after myocardial infarction and reduce ventricular dilation (Fig. 4B).[62] In summary, pericardial injection, as a safe and effective delivery method, has opened up new avenues for hydrogel-based cardiac repair treatment strategies.

Gelatin was dissolved in a phosphate buffer solution and reacted with methacrylic anhydride. A photoinitiator was then added, and under UV irradiation, the methacrylate groups underwent free radical polymerization to form a covalently crosslinked gelatin methacrylate (GelMA) hydrogel. Endothelial progenitor cells (ECFCs) and mesenchymal stem cells (MSCs) were resuspended in a liquid GelMA precursor solution. The GelMA precursor solution containing cells was injected into the myocardial infarction area and formed a gel *in situ* through UV irradiation. GelMA was derived from natural gelatin, and its degradation products were non-toxic gelatin peptides, thereby avoiding inflammatory reactions. The moderate cross-linking degree of the GelMA hydrogel mimicked the natural myocardial state, promoting the survival and vascularization of ECFCs and MSCs. ECFCs and MSCs in GelMA hydrogels upregulated TGF-β1 expression, promoted NR (pro-regenerative neutrophils) polarization, and promoted M2 macrophage polarization, thereby inhibiting inflammatory responses. Additionally, they promoted myocardial tissue repair by secreting VEGF (vascular endothelial growth factor) and IL-4 (Interleukin-4). Furthermore, ECFCs and MSCs in the hydrogel improved myocardial perfusion and reduced cardiac fibrosis. In summary, the injection of GelMA hydrogel-encapsulated ECFCs and MSCs into the myocardial infarction area significantly improves cardiac function after myocardial infarction, offering potential contributions to the treatment of acute myocardial infarction (Fig. 4C).[93]

2.4 Hydrogel with immunomodulatory function

In the therapeutic field of myocardial infarction, hydrogels offered a new perspective on immunomodulation with their unique biomaterial properties. Inflammatory response after myocardial infarction was a critical part of the heart repair process, and hydrogel served as an intelligent platform for immune regulation, precisely influencing the activity and distribution of immune cells through its tunable physicochemical properties.[94,95] They were designed to release anti-inflammatory factors or cytokines to attenuate excessive inflammatory responses while promoting the infiltration of beneficial immune cells, such as M2-type macrophages, thereby creating a microenvironment conducive to myocardial repair.[96–98] In addition, hydrogels were used as carriers to deliver factors with immunomodulatory properties to further enhance therapeutic effects.[99] For example, the MMP-responsive hydrogel delivery system (MPGC4) was able to release anti-inflammatory factors on demand, which significantly reduced the degree of fibrosis after MI.[97] In this way, the hydrogel not only inhibited the harmful immune response, but also promoted the regeneration and functional recovery of the injured myocardium, opening up an innovative path for immunotherapy of myocardial infarction. In addition, Table 6 showed a comparison of the advantages and disadvantages of the two immunomodulatory hydrogels in the treatment of myocardial infarction.

A study has developed a novel composite hydrogel material with immune-modulating properties, composed of two marine-derived natural biomaterials: melanin nanoparticles (MNPs) extracted from cuttlefish ink and alginate (Alg). Alg was an anionic polysaccharide whose molecular chain contained guluronate, which formed a cross-linked network structure with adjacent polymer chains through divalent calcium ions (Ca^{2+}). The calcium ion-crosslinked alginate network provided mechanical support. This gave MNPs/Alg hydrogels moderate mechanical strength. Moderate mechanical strength helped coordinate myocardial contractions, promoted cardiac function reconstruction and avoided mechanical stress caused by excessive stiffness. In addition, the addition of MNPs increased the roughness of the hydrogel surface. The rough surface promoted the adhesion of cardiomyocytes (CMs) and enhanced the repair effect. The alginate gel gradually degraded through ion exchange between Ca^{2+} and Na^{+} in body fluids and completely dissolved within 21 days, avoiding the cytotoxicity of high concentrations of MNPs. The reductive functional groups contained in MNPs/Alg hydrogels, such as phenolic hydroxyl groups and DPPH radicals, scavenged ROS. This was the core mechanism by which the hydrogel exerted its functional effects. In the process of scavenging ROS, MNPs/Alg hydrogels upregulated the expression of c-TnT and Cx43, while simultaneously

Table 6 Comparison of the advantages and disadvantages of two types of immune-modulating hydrogels in the treatment of MI

Hydrogel type	Core strengths	Main limitations	Applicable scenarios	References
MNPs/Alg hydrogel	Natural antioxidant, immune modulator, angiogenesis	Uncontrollable degradation, no targeted release capability	Antioxidant and inflammatory regulation in acute myocardial infarction	100
MPGC4 hydrogel	MMP responsive gene release, precise immune reprogramming	Complex synthesis, potential toxicity under ultraviolet light	Chronic MI repair requiring long-term immune regulation	97

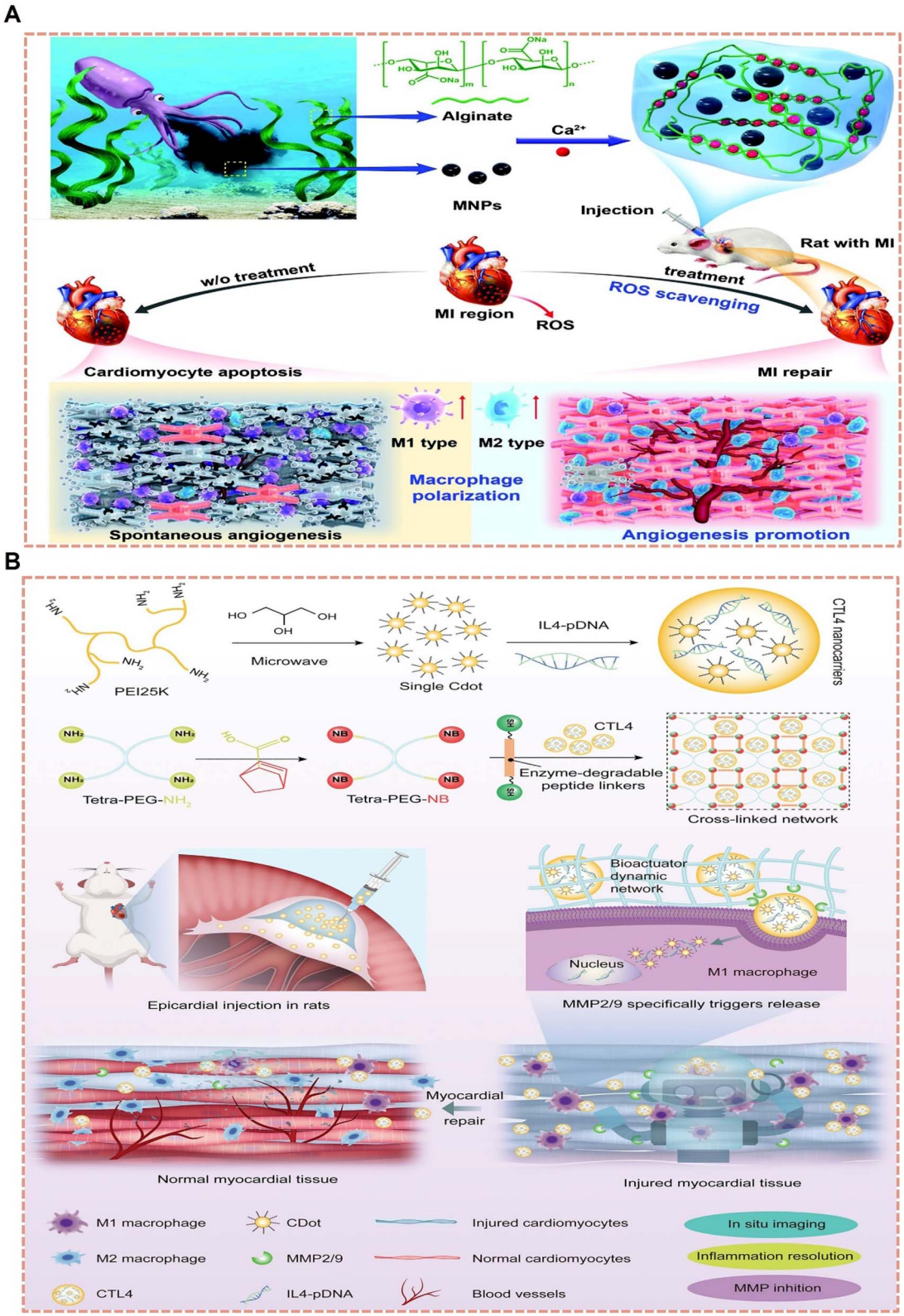

Fig. 5 Hydrogel with immunomodulatory propertie. (A) Mechanisms by which MNPs/Alg hydrogels promote macrophage polarization toward the M2 phenotype with regenerative functions.[100] (B) Principles of MPGC4 hydrogel to promote polarization of inflammatory M1 macrophages to anti-inflammatory M2 subtypes in myocardial infarction.[97]

inhibiting the expression of the apoptotic gene Caspase-3, thereby protecting cardiomyocytes from oxidative stress-induced damage. Additionally, MNPs/Alg hydrogels regulated the ROS microenvironment, activated the PI3K/Akt1/mTOR signaling pathway, and promoted the polarization of macrophages from pro-inflammatory M1 type to anti-inflammatory M2 type. The reduction in M1-type macrophages was manifested by decreased levels of TNF-α, iNOS, and CD86. Increased levels of IL-10, TGF-β, Arg1, and CD206 indicated an increase in M2-type macrophages. Furthermore, MNPs/Alg hydrogels improved endothelial cell survival by scavenging ROS, thereby promoting the restoration of myocardial blood supply. Increased endothelial cell survival upregulates the expression of angiogenesis-related genes (VWF, VCAM1, CD31) (Fig. 5A).[100] In summary, the functions of MNPs/Alg hydrogels were mainly manifested as follows: scavenging ROS and directly protecting cardiomyocytes through antioxidant effects; polarizing macrophages by regulating the PI3K/Akt pathway; promoting angiogenesis to improve blood supply; and synergistically repairing fibrosis and restoring cardiac function.

In response to the complex microenvironmental characteristics after MI, researchers have developed an MMP2/9-responsive hydrogel system (MPGC4). The system consisted of a tetrapolyethylene glycol (PEG) hydrogel and a composite gene nanocarrier (CTL4), in which CTL4 couples carbon dots (CDot) to interleukin 4 (IL-4) plasmid DNA *via* electrostatic interactions (Fig. 5B).[97] Tetra-PEG-NH2 and MMP-sensitive peptides were dissolved in CTL4 solution, followed by the addition of a photoinitiator. Under 365 nm UV light, the thiols on the MMP-sensitive peptide chains underwent a click reaction with the vinyl groups of *tetra*-PEG-NB, forming a cross-linked hydrogel system MPGC4. The design of MPGC4 fully utilized the characteristic of upregulated MMP2/9 expression in the post-MI microenvironment to achieve on-demand release of CTL4, thereby precisely regulating the immune microenvironment of the infarct area and avoiding off-target toxicity. The entanglement of polymer chains in *tetra*-PEG conferred shear thinning properties to the hydrogel, enabling the MPGC4 hydrogel to adapt to the shear forces of cardiac contractions and prevent leakage after injection. The surface modification of carbon dots (CDots) in CTL4 with PEI25k not only enhanced the stability and gene loading capacity of the hydrogel but also facilitated real-time tracking of CTL uptake by macrophages and hydrogel retention in the myocardium. The primary mechanism by which CTL4 exerted its function was through regulating macrophage polarization. Following myocardial infarction, increased expression of MMP2/9 triggers hydrogel degradation, releasing CTL4. Subsequently, CTL4 was internalized by M1-type macrophages, and IL4-pDNA expressed IL-4. IL-4 upregulated M2 markers (CD206, Arg1) and downregulated M1 markers (CD86, TNF-α) through the STAT6 signaling pathway, thereby achieving the polarization of M1 macrophages to M2 macrophages. M2 macrophages secreted TGF-β and IL-10, which inhibited inflammatory damage to cardiomyocytes. Simultaneously, they secreted pro-angiogenic factors (such as VEGF), increasing the density of $CD31^+$ neoangiogenesis, thereby improving ejection fraction and cardiac function (Fig. 5B).[97] These results indicated that the MPGC4 system modulated the post-MI immune microenvironment through multi-target regulation, providing a novel smart delivery strategy for the treatment of myocardial infarction.

2.5 Hydrogel with detection function

In the field of diagnosis and monitoring of myocardial infarction, hydrogels were an innovative detection tool due to their unique physicochemical properties and biocompatibility. These smart hydrogels visually reflected the extent of myocardial damage and the repair process through changes in color,[101] transparency,[102] or electrical conductivity. In addition, the hydrogels were integrated with biosensors or nanotechnology for real-time monitoring of the functional status and pathological changes of cardiomyocytes, providing important information for early diagnosis and condition assessment.[82,103,104] By combining hydrogel with microelectronic technology, an implantable monitoring system could be developed to realize long-term tracking of the cardiac status of myocardial infarction patients.[105] This hydrogel-based detection technology not only improved the accuracy and timeliness of diagnosis, but also provided a scientific basis for the development of personalized treatment plans, which greatly promoted the development of myocardial infarction diagnostic and treatment technology. In addition, Table 7 showed a comparison of the advantages and disadvantages of the two types of hydrogels in detecting cardiac function.

In recent years, significant progress has been made in the application of hydrogel materials in biomedical fields, with the development of multifunctional hydrogel sutures being particularly noteworthy. Diagnostic, Therapeutic, and Monitoring Sutures (DTMS), a new type of smart hydrogel suture, integrated

Table 7 Comparison of the advantages and disadvantages of two types of hydrogels in cardiac function testing

Hydrogel type	Core strengths	Main limitations	Applicable scenarios	References
DTMS suture hydrogel	Integrated treatment and monitoring, high mechanical strength	Dependence on external pumping results in insufficient long-term stability of PPy	Postoperative real-time monitoring and drug combination therapy	106
$SPE_2NC_{2\cdot5}$ hydrogel	Highly sensitive infarction localization, immune-friendly	No drug release function, complex synthesis	Long-term monitoring and pathological assessment of chronic myocardial infarction	109

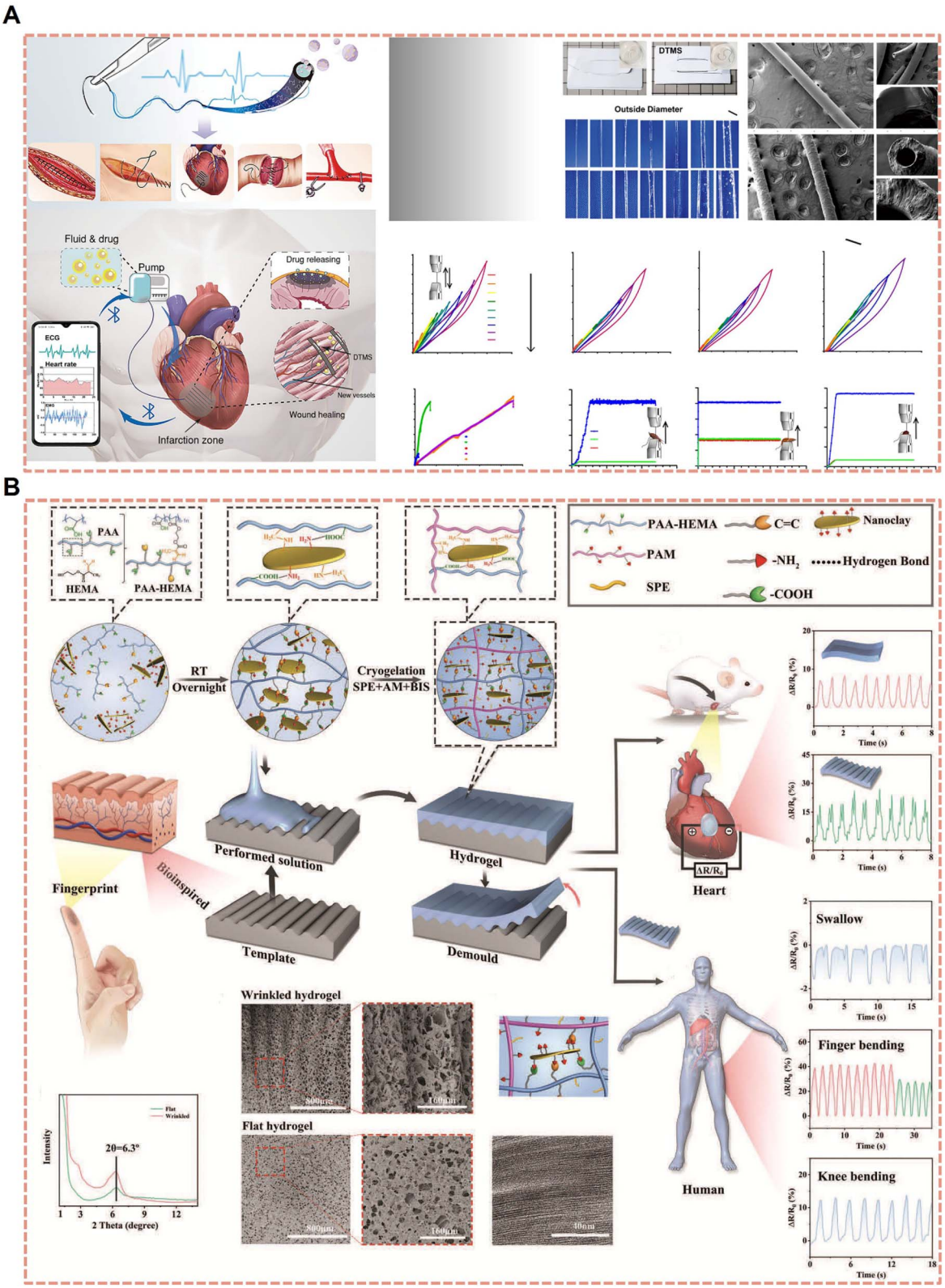

Fig. 6 Hydrogel for detection function. (A) Schematic diagram of the DTMS hydrogel suture for on-demand detection of cardiac function.[106] (B) Mechanistic mapping of nanoclay composite-based hydrogels for precise localization of regions of MI and real-time detection of pathological changes.[109]

real-time signal sensing, on-demand monitoring, and drug delivery, providing an innovative solution for postoperative wound management (Fig. 6A).[106] The synthesis of DTMS was based on biocompatible poly (vinyl alcohol) (PVA), deprotonation of the PVA hydroxyl group by alkali treatment, followed by the formation of complexes between the O-groups and free radicals, which promoted the stretching and alignment of the PVA chains, and consequently the construction of crystalline structural domains (Fig. 6A).[106] When in contact with water, hydrogen bonding replaced the complexation of the PVA chains to form stable crystalline structural domains. This process, the formation of microcrystals and the establishment of hydrogen bonds prompted the expulsion of water molecules, resulting in the formation of hydrogels with low swelling and high mechanical strength. Hydrogen bonds and microcrystalline domains provided high mechanical strength, making DTMS stronger than traditional silk and nylon threads. DTMS's high elasticity and low friction made it more suitable for the dynamic environment of the heartbeat and reduced cardiac damage. The uniformly dispersed polypyrrole (PPy) in DTMS gave the hydrogel conductivity (conductivity 1.47 S cm^{-1}), enabling it to sense signals. The unique design of DTMS hydrogel enabled it to have bidirectional microchannel functionality. Microchannels enabled the quantitative delivery of the drug SNAP *via* a micro pump, which suppressed inflammation by downregulating the expression of IL-6 and TNF-α, while promoting the expression of CD31 to improve ejection fraction and alleviate myocardial ischemia. Conductive PPy enabled the hydrogel to capture bioelectric signals (such as electrocardiogram (ECG) and electromyogram (EMG)) and transmitted the data to mobile devices *via* Bluetooth (Fig. 6A).[106] This multifunctional hydrogel suture, which combined diagnosis, treatment, and monitoring, provided new technical means for postoperative tissue repair and chronic disease management, and had broad clinical application prospects.

In recent years, hydrogel materials have shown great potential for application in the field of biosensors, especially in wearable devices[107] and real-time pathology monitoring.[108] This study developed a novel strain biosensor based on nano-clay composite hydrogel (SPE2NC2.5) for precise localization of myocardial infarction areas and real-time detection of pathological changes (Fig. 6B).[109] Crosslinking polyacrylamide (PAM)/amphoteric ion monomer (SPE)/*N*,*N*-methylbisacrylamide (BIS) to form a primary polymer network structure. Multifunctional crosslinking agents and nano-reinforced clay flakes (surface-modified with polyacrylic acid-hydroxyethyl methacrylate (PAA-HEMA)) were added to the primary polymer network, embedded into the polymer network *via* radical polymerization, forming nano-clay composite hydrogels (SPE2NC2.5). The positively charged amino groups in nanoclay and the negatively charged carboxyl groups in PAA were attracted to each other through electrostatic forces, enhancing their bonding. In the zwitterionic structure of SPE, the sulfonate groups and quaternary ammonium groups stabilized the hydrogel network through hydrophilic–hydrophobic interactions. The nanoclay layers enhanced mechanical properties through physical entanglement and restriction of polymer chain movement. The high elasticity of nanoclay matched the softness of cardiac tissue, reducing mechanical mismatch during implantation. The zwitterionic ions in the SPE2NC2.5 hydrogel provided conductivity, inhibited specific protein adsorption, and promoted M2 macrophage polarization. The hydrogel captured cardiac mechanical movements through ionic conductivity, converted them into resistance changes, and output waveforms similar to electrocardiograms (Fig. 6B).[109] In summary, this material has been proven for the first time to accurately locate the area where myocardial infarction occurs. This breakthrough discovery provides a new strategy for real-time monitoring of pathological changes in the heart. In addition, the development of this new hydrogel material has brought new possibilities to the field of biomedical sensing, especially in the monitoring and diagnosis of cardiovascular diseases, where it has important application prospects.

2.6 Other hydrogels

MI was a serious cardiovascular disease usually caused by blockage of coronary arteries, resulting in myocardial ischemia and necrosis.[110,111] Conventional treatments such as medications and surgeries alleviated the symptoms, but it was difficult to achieve complete repair of myocardial tissue.[112] In recent years, 3D-printed hydrogels and microfluidic hydrogels have opened up new possibilities for myocardial repair.[113,114] 3D-printed hydrogels belonged to the category of functional structural hydrogels, which focused on macro-customization and mechanical support, and were applied to tissue engineering scaffolds (heart patches).[115] Microfluidic hydrogels belonged to dynamic functional hydrogels, which were mainly used for micro-scale control and high-throughput operations.[116] Combined with microfluidic technology, hydrogels constructed complex microvascular networks to improve blood supply in ischemic areas, thus providing new strategies for the treatment of myocardial infarction.[117] Therefore, this section mainly discussed the functions of 3D-printed hydrogels and microfluidic hydrogels in MI.

In the field of myocardial repair materials, researchers have developed a customized cardiac patch with a double-layer structure by integrating two genetically engineered cleaved leucine zipper protein hydrogel layers using 3D printing technology. From a structural design perspective, the cardiac patch consisted of two complementary hydrogel layers. The inner layer (ASP hydrogel) formed reversible physical cross-links through hydrophobic interactions between the leucine zipper domains (A/A and P/P), giving it a soft mechanical strength similar to that of natural heart tissue and enabling strong interface adhesion with heart tissue. Additionally, this layer exhibited excellent *in vivo* biocompatibility and controlled biodegradability, making it an ideal minimally invasive material for heart tissue contact. The outer layer (A35m hydrogel) consisted of ASP fused with mussel foot proteins Mefp3 and Mefp5 containing equimolar amounts of dopa. The dopa residues were oxidized to form quinones, triggering covalent crosslinking, while cation-π, π–π interactions, and hydrogen bonds also exist, significantly enhancing the mechanical strength and

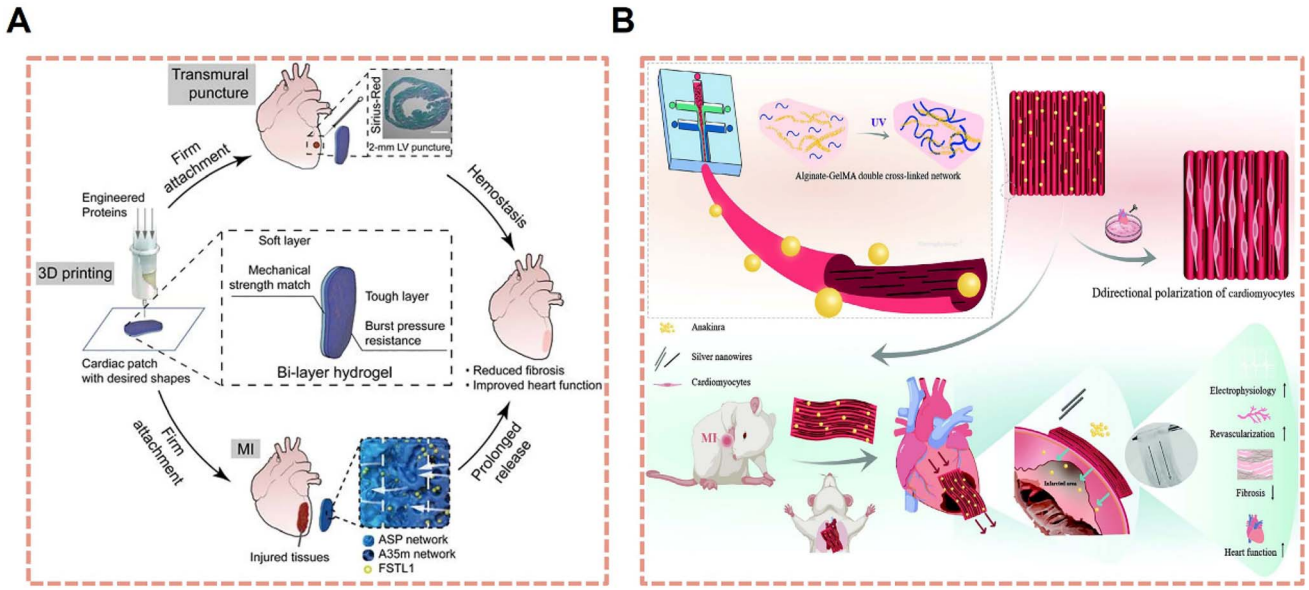

Fig. 7 Other functions of hydrogels. (A) 3D-printed hydrogel heart patches were used to improve cardiac function after MI.[118] (B) Flow chart of alginate-methacrylic acid gelatin hydrogel combined with microfluidics for cardiac recovery after MI.[114]

cohesion of the hydrogel. The dense porous structure of the outer hydrogel not only provided stronger cohesion but also enabled the loading of FSTL1. Additionally, by adjusting the Mefp-3/5 ratio or Dopa content, the adhesion strength and modulus of the hydrogel could be precisely controlled to match the requirements of different tissues. Notably, due to the self-healing properties of ASP hydrogels, two layers of different hydrogels were seamlessly integrated. Subsequently, 3D printing technology was used to fabricate a cardiac patch from the dual-layer hydrogel (Fig. 7A).[118] The high adhesion of the A35m layer directly sealed ventricular perforations, while the flexibility of the ASP layer reduced mechanical stimulation of the myocardium. The sustained release of FSTL1 in the cardiac patch inhibited fibroblast activation, and reduced scar area. Conversely, FSNL1 enhanced myocardial cell proliferation (increased $pH3^+$ cells), and improved cardiac ejection fraction (EF) and shortening fraction. These effects result in the 3D-printed hydrogel cardiac patch significantly improved cardiac function post-myocardial infarction.

In recent years, multifunctional anisotropic cardiac patches prepared using microfluidic technology have shown broad application prospects in the field of cardiac tissue engineering. Researchers have successfully developed alginate-methyl acrylate gelatin hydrogel patches by innovatively integrating microfluidic technology, ion beam crosslinking, and parallel packaging. The microfluidic design employed a three-channel cross-type PDMS chip. The middle channel was injected with a pre-gel solution containing sodium alginate (Alginate), methyl acrylate gelatin (GelMA), silver nanowires (AgNWs), and a photoinitiator. The two side channels were filled with calcium-free D-PBS and low-concentration $CaCl_2$ solutions, respectively. Sodium alginate formed an initial gel by binding with Ca^{2+}. Light-initiated polymerization of methacrylate groups formed a permanent hydrogel. Silver nanowires were arranged in a directional pattern using microfluidics to form conductive pathways, promoting the conduction of cardiac electrical signals. By adjusting the ratio of alginate to GelMA and the concentration of AgNWs, the hydrogel was made to better match the stiffness of the infarcted myocardium, thereby inhibiting ventricular remodeling. Additionally, silver nanowires had antibacterial effects, reducing the risk of surgical infection. Furthermore, the conductive hydrogel composed of AgNWs promoted endothelial cell migration, increased blood flow perfusion in the infarcted area, and reduced the infiltration of $CD45^+$ inflammatory cells. The loading of Anakinra in microfluidic hydrogels reduced the expression of inflammatory factors IL-6 and TNF-α, thereby decreasing myocardial fibrosis (Fig. 7B).[114] These outstanding properties of microfluidic hydrogels made them ideal candidate materials for cardiac tissue repair. In addition, this study provided a new example of the innovative application of microfluidic technology in the field of tissue engineering, opening up new research directions for addressing complex tissue engineering challenges in the future.

3 Summary and outlook

Hydrogel materials show great potential in myocardial infarction therapy, and their versatility provides a new solution for myocardial repair. As drug delivery vehicles, hydrogels enable controlled release of drugs, improving therapeutic efficacy and reducing side effects. For stem cell and exosome delivery, hydrogels provide a suitable microenvironment for cells and bioactive molecules, promoting cell survival, differentiation and function. Its detection function realizes real-time monitoring of the myocardial microenvironment by integrating sensing elements, providing the possibility of personalized treatment. In addition, the electrical conduction properties of hydrogels

can improve the transmission of myocardial electrical signals and support the recovery of cardiac function. Through the microenvironmental regulation function, hydrogel mimics the properties of natural extracellular matrix, creating conditions for cell proliferation and tissue regeneration. Combined with tissue engineering and microfluidic technology, the hydrogel further realizes the construction of complex tissue structure and the formation of microvascular network, which provides a new idea for the blood flow reconstruction of ischemic myocardium.

Despite the remarkable progress of hydrogels in myocardial infarction therapy, many challenges remain. First, the mechanical properties and degradation rate of hydrogels need to be further optimized to match the dynamic demands of myocardial tissues. Second, how to realize the precise regulation and synergistic effect of multifunctional hydrogels still requires in-depth research. In addition, the long-term biosafety and immunocompatibility of hydrogels need to be systematically evaluated. In the future, with the cross-fertilization of materials science, bioengineering and medicine, hydrogel materials are expected to achieve wider applications in myocardial infarction treatment and bring revolutionary breakthroughs in the treatment of cardiovascular diseases.

Author contributions

H. Z. contributed to the conception of the article and writing – original draft; J. S. contributed to the editing of this article; Y. C., and B. Z. contributed to funding acquisition, writing – review and editing. All the authors have read and agreed to the published version of the manuscript.

Conflicts of interest

The authors declare no competing financial interest.

Data availability

This review does not include any original research results, software, or code, and no new data was generated or analyzed during the review process.

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