Wu and Liu *NPG Asia Materials* (2022) 14:9
https://doi.org/10.1038/s41427-021-00330-y

NPG Asia Materials

REVIEW ARTICLE Open Access

Functional hydrogels for the treatment of myocardial infarction

Tengling Wu[1] and Wenguang Liu[1]

Abstract

Myocardial infarction (MI) is a major disease posing a significant threat to human health, as it leads to necrosis of numerous cardiomyocytes (CMs), left ventricle dilation, and cardiac dysfunction, ultimately resulting in heart failure. Owing to the shortage of heart donors and the shortcomings of current clinical treatment methods, significant resources have been dedicated to developing platforms for cardiac tissue engineering, including functional hydrogels. Herein, we review variations in the myocardial microenvironment and the effects of functional hydrogel systems that are designed to support and mimic this microenvironment during cardiac repair following MI. Specifically, we provide an overview of recent functional hydrogels designed for cardiac tissue engineering. These include matrix metalloproteinase-responsive hydrogels, reactive oxygen species-scavenging hydrogels and immunomodulatory hydrogels, which can reverse the adverse myocardial microenvironment. Additionally, we describe conductive hydrogels that can reconstruct electrical signal conduction within infarct areas, vascularized hydrogels that promote the repair of cardiac function, and 3D-printed hydrogels, which can achieve personal customized cardiac tissue via printing of intact cardiac structures, thus addressing the current shortage of heart donors.

Introduction

According to the American Heart Association, cardiovascular diseases, especially myocardial infarction (MI), which is the consequence of coronary artery occlusion, are the primary causes of death and disability worldwide[1–3]. Coronary artery occlusion impedes the transportation of oxygen and nutrients, ultimately leading to the death of numerous CMs[4–7]. Moreover, the limited regenerative capacity of CMs in adult myocardial tissue significantly limits their self-repair function[8,9], leading to ventricle maladaptive remodeling, including thinning of the ventricular wall, scar tissue formation, and ultimately heart failure[10–12]. Currently, coronary bypass surgery and pharmacological approaches are common clinical treatment options for MI. However, these methods only serve to delay the process of ventricular remodeling without restoration of the infarcted myocardium[13–15]. Therefore, an urgent need exists for new, improved treatment strategies to facilitate the repair of dysfunctional heart tissues[16].

Following MI, numerous changes occur within the myocardial microenvironment, including fluctuations in the abundance of matrix metalloproteinases (MMPs)[17,18], reactive oxygen species (ROS)[19,20], and inflammatory factors[21,22]. In normal myocardial tissue, MMPs and tissue inhibitors of matrix metalloproteinases (TIMPs) are in a dynamically balanced state;[23] however, the overexpression of MMPs following MI can destroy the extracellular matrix (ECM) of myocardial tissue, leading to adverse remodeling of the left ventricular wall[24,25]. Similarly, ROS are overexpressed in the infarcted myocardium, which disrupts cellular homeostasis, causing damage to CMs while promoting inflammation and myocardial fibrosis[26,27]. The excessive activation of inflammation can lead to maladaptive healing and ventricular remodeling[28]. In addition, the reduced oxygen and nutrient supply caused by coronary artery occlusion can lead to the development of fibrous scar tissue, thus increasing the resistivity of myocardial tissue and

Correspondence: Wenguang Liu (wgliu@tju.edu.cn)
[1]School of Materials Science and Engineering, Tianjin University, Tianjin 300350, China

hindering electrical signaling between CMs[4,29,30]. Therefore, to reverse this adverse microenvironment, reconstruction of electrical signal conduction and/or promotion of angiogenesis in the infarct area can facilitate the repair of cardiac function.

Hydrogels, which are soft, moist materials with properties similar to those of human soft tissues, are widely used in tissue engineering[31]. In fact, studies have shown that hydrogels not only provide mechanical support during myocardial tissue repair[32,33] but also serve as carriers for cell or drug delivery[34,35]. With the ever-increasing knowledge regarding variations in the myocardial microenvironment following MI, intelligent and functional hydrogels have been synthesized for use during cardiac repair processes. For example, MMP-responsive hydrogels[36,37], ROS-scavenging hydrogels[38,39], and immunomodulatory hydrogels are used to regulate the abundance of MMPs, ROS, and inflammation, respectively, in infarcted areas. Meanwhile, conductive hydrogels[40,41] are used to enhance the electrical coupling between CMs, and proangiogenic hydrogels[42,43] are used to promote angiogenesis in infarcted areas. Moreover, hydrogels are used to mimic the natural myocardial structure through 3D printing technology to repair the myocardium or print intact myocardium to replace necrotic tissue[44,45].

In this review, we briefly discuss the variations that occur within the cardiac microenvironment following MI and summarize the synthesized functional hydrogels based on these variations to reverse the adverse myocardial microenvironment or promote recovery of cardiac function (Fig. 1). Finally, we present potential future directions for the design of effective hydrogels for MI treatment. This review is expected to provide an improved understanding of the microenvironment associated with infarcted myocardium and suitable hydrogels for treating MI.

MMP-responsive hydrogels

MMPs are members of the zinc endopeptidase family that cleave ECM components[46]. Thus, the overexpression of MMPs after MI can disrupt the balance between MMPs and TIMPs[23], leading to degradation of the ECM and decreased mechanical properties of the ventricular wall, subsequently causing progressive thinning and global dilatation of the ventricular wall in the infarcted area[24]. Indeed, MMPs have been described as the driving force behind myocardial matrix remodeling[25], with MMP abundance positively correlated with MI severity, which is also used as a marker of heart failure[47]. Therefore, the targeted inhibition of MMP expression and activity is of great significance for the prevention of heart failure after MI. The most common methods to reduce MMP activity include pharmacologic options, such as MMP inhibitors and transgenic constructs[48]. However, most MMP inhibitors are small organic molecules with active zinc-chelating groups, such as hydroxylamine[49] or mercaptan[50], which may cause cardiac fibrosis[51]. Meanwhile, the use of transgenic methods to knock out specific genes related to MMP expression causes long-term effects rather than a regulatory mechanism for reducing the overexpression of MMPs following MI[52]. Therefore, designing hydrogels capable of regulating MMP levels, thus inhibiting myocardial remodeling after MI, has become a popular design strategy.

Carlini et al.[53] designed a circular peptide based on the overexpression of MMP-2/9 and elastase enzymes after MI (Fig. 2a). They reported that cyclic peptide progelators flow freely in solution but become linear and self-assemble into hydrogels under the action of MMP-2/9 and elastase enzymes (Fig. 2b). The results of histological and fluorescence analyses demonstrated that the cyclic peptide progelators assembled into hydrogels after injection into the infarcted myocardium (Fig. 2c). Their low viscosity in vitro and gelling properties at the site of infarcted myocardium facilitate the delivery of hydrogels or therapeutic factors to the heart via minimally invasive techniques. In fact, Guan et al.[54] developed a peptide-based MMP-2 inhibitor delivery system by combining a PNIPPAm-based hydrogel with the MMP-2-specific inhibitor peptide CTTHWGFTLC (CTT). CTT is simply mixed with hydrogel solutions before treating MI. The results showed that the hydrogel with CTT could reduce the concentration of MMP-2 in the infarcted area, thus preventing the degradation of ECM, including preserved ventricular wall thickness and collagen composition, reduced adverse remodeling of the ventricles, and improved cardiac function. Although hydrogels loaded with MMP-2 inhibitors have achieved certain efficacy in treating MI, they are only capable of slowly releasing inhibitors, without controlled release properties in response to changes in MMP abundance within the myocardial environment. By comparison, Burdick et al[55]. developed an MMP-responsive hydrogel in which TIMP-3 was immobilized by electrostatic action and released via degradation of the hydrogel to reduce the level of MMPs. The hydrogel was synthesized by simple mixing of aldehyde-modified hyaluronic acid (HA-ALD), aldehyde-modified dextran sulfate (DS-ALD), and hydrazine-modified and peptide-including MMP-cleavable sequence embedded HA (HA-peptide-HYD). Dextran sulfate mimics the structure of heparin, which has a strong binding capacity with TIMP-3. Thus, TIMP-3 is fixed in the hydrogel to prevent its passive diffusion. The MMP-cleavable peptide is modified by a sulfhydryl group and a hydrazide group at either end. The sulfhydryl groups react with maleimide-functionalized HA, while hydrazide groups, on the opposite end, react with

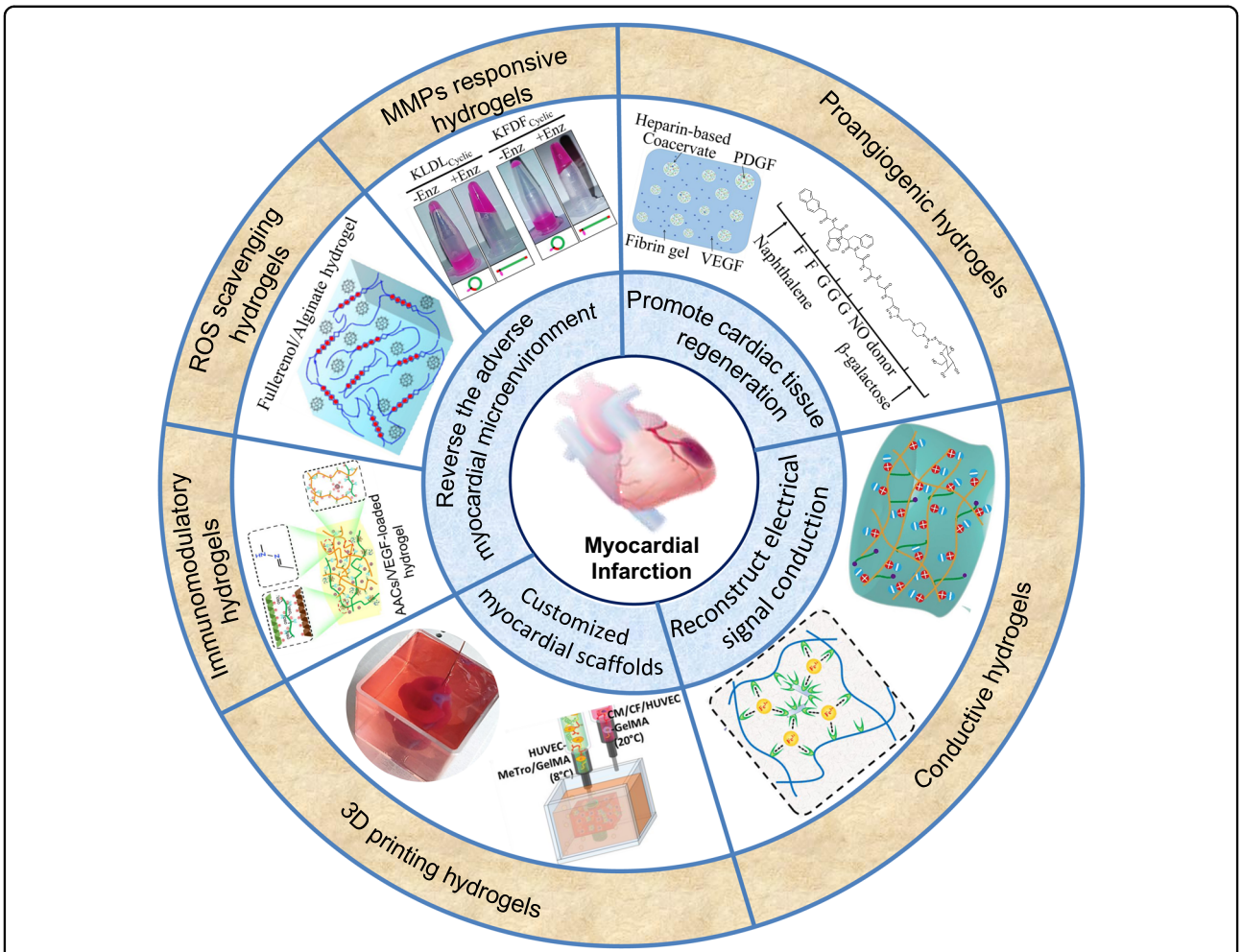

Fig. 1 Different hydrogels used for treating MI. Schematic illustration of the preparation of different hydrogels for treating MI, such as MMP-responsive hydrogels, Copyright 2019, Nature Publishing Group (ref. [53]); ROS-scavenging hydrogels, Copyright 2017, American Chemical Society (ref. [65]); immunomodulatory hydrogels, Copyright 2021, Elsevier Science (ref. [78]); conductive hydrogels, Copyright 2020, American Chemical Society (ref. [12]), Copyright 2021, Elsevier Science (ref. [97]); proangiogenic hydrogels, Copyright 2015, Elsevier Science (ref. [99]), Copyright 2015, Elsevier Science (ref. [104]) and 3D-printed hydrogels, Copyright 2020, Wiley & Sons Inc. (ref. [109]), Copyright 2019, Wiley & Sons Inc. (ref. [110]).

aldehyde-containing polymers to form hydrogels through the Schiff base reaction. Magnetic resonance imaging after 14 days revealed that, following injection of this hydrogel into the myocardium, it disappeared in the MI group, in which MMPs were overexpressed, but it remained visible in the normal group, clearly demonstrating that the degradation behavior of the hydrogel was responsive to the increased MMP activity in MI tissue. In vivo experiments further demonstrated that this bioresponsive hydrogel carrying TIMP-3 significantly inhibited the activity of MMPs after MI and effectively inhibited left ventricular adverse remodeling. Thus, the design of this MMP-degradable hydrogel facilitates the release of TIMPs according to the level of MMPs in infarcted myocardia, thereby reducing any off-target effects of TIMPs. Similarly, in a recent study, Dai et al[56]. designed an intelligent hydrogel capable of responding to MMP-2/9 expression within infarcted areas and releasing growth factors. The hydrogel is composed of two components, glutathione (GSH)-modified collagen hydrogel (collagen-GSH) and a recombinant protein comprising basic fibroblast growth factor (bFGF), glutathione *S*-transferase (GST), and MMP-2/9 cleavable peptide PLGLAG (TIMP). Among them, TIMP represents the most competitive substrate for the cardiac extracellular matrix and is thus cleaved via MMP-2/9 activity to protect the cardiac extracellular matrix from MMP degradation while also causing the release of bFGF. Thus, TIMP can reduce MMP abundance and release growth factors on demand. The animal experiment results further demonstrated that rats treated with TIMP-containing hydrogels had the thickest

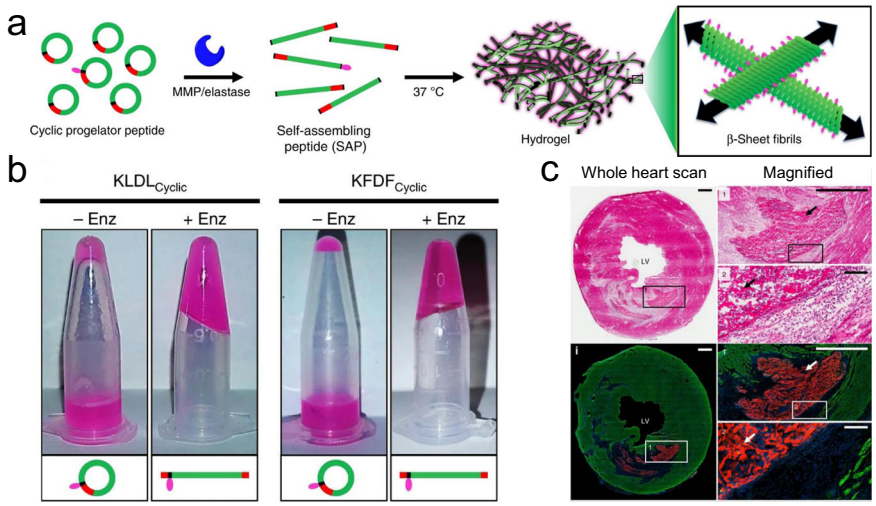

Fig. 2 MMP-responsive hydrogels used for treating MI. a Schematic of cyclic, enzyme-responsive progelator peptides for activatable gelation. **b** States of KLDL$_{Cyclic}$ and KFDF$_{Cyclic}$ progelators before and after enzyme treatment. **c** Hematoxylin and eosin (H&E) staining of the heart after injecting peptide material into infarcted myocardium. Copyright 2019, Nature Publishing Group (ref. [53]).

ventricular walls and minimal collagen deposition following MI, indicating that MMPs respond to these hydrogels, which could effectively reduce cardiac remodeling. These MMP-responsive hydrogels are also predicted to be effective for the treatment of ischemic heart disease.

A large amount of ROS accumulates in the infarcted myocardium after MI[26], which can directly attack DNA, proteins, and cell membranes and can thus also cause the death of myocardial cells and vascular cells in noninfarcted areas, resulting in additional heart damage and increasing the infarct size[27]. In addition, ROS can stimulate the production of proinflammatory cytokines by activating multiple pathways; these cytokines can further stimulate the production of ROS, causing a vicious cycle[27]. Therefore, reducing the level of ROS in the infarcted myocardium plays an important role in the heart remodeling process after MI. Previous studies have shown that ROS-scavenging of biomaterials can protect CMs and improve cardiac function by eliminating excess ROS; among these, numerous hydrogels with antioxidant properties were used in the treatment of MI, and their therapeutic effects were investigated[57,58]. There are two types of ROS-scavenging hydrogels: one is loaded with antioxidants, while the other is a self-antioxidative hydrogel.

To reverse the adverse microenvironment created following MI, our research team developed a series of ROS-sensitive hydrogels. For example, a novel ROS-sensitive hyperbranched macromer (HB-PBAE) was synthesized by employing polyethylene glycol diacrylate (PEGDA) and cystamine (Fig. 3a)[59]. The HB-PBAE polymer could effectively scavenge 1,1-diphenyl-2-picrylhydrazyl (DPPH) radicals (Fig. 3b) and form ROS-sensitive hydrogels with thiolate-modified hyaluronic acid (HA-SH) through Michael addition. The obtained hydrogel exhibited H_2O_2-responsive degradation behavior. Meanwhile, a novel nanoparticle (DMOG@PDA-EGCG) with ROS-scavenging ability was synthesized in our research by connecting the polyphenol epigallocatechin-3-gallate (EGCG) to polydopamine (PDA) nanoparticles through π-π interactions[60]. DMOG@PDA-EGCG nanoparticles could crosslink with HA-SH to form hydrogels based on the Michael addition reaction between the oxidized quinone form of PDA and the thiol group of HA-SH. This hydrogel could rapidly release EGCG, accelerate the capture ability of ROS, and reverse the adverse cardiac microenvironment after MI. Furthermore, Gao et al[61]. developed an ROS-responsive hydrogel through the combination of ROS-cleavable hyperbranched polymers (HBPAK) and methacrylate HA (HA-MA). HBPAK was synthesized via a Michael addition reaction between PEGDA with a molecular weight of 575 (PEGDA575) and thioketal diethyl amine. The ROS-scavenging capacity of the hydrogel could be adjusted by altering the concentration of HBPAK, and the hydrogel could effectively remove excessive ROS after MI. The development of such biocompatible ROS-sensitive hydrogels is of great importance for improving the MI microenvironment.

In addition, the effects of ROS-scavenging hydrogels on CMs and cardiac function have also been reported. For example, Wagner et al[62]. incorporated 4-amino-2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) groups as ROS-scavenging pendants into a poly-N-isopropylacrylamide (NIPAAm)-based hydrogel. The TEMPO-containing hydrogel could effectively scavenge ROS radicals, inhibit

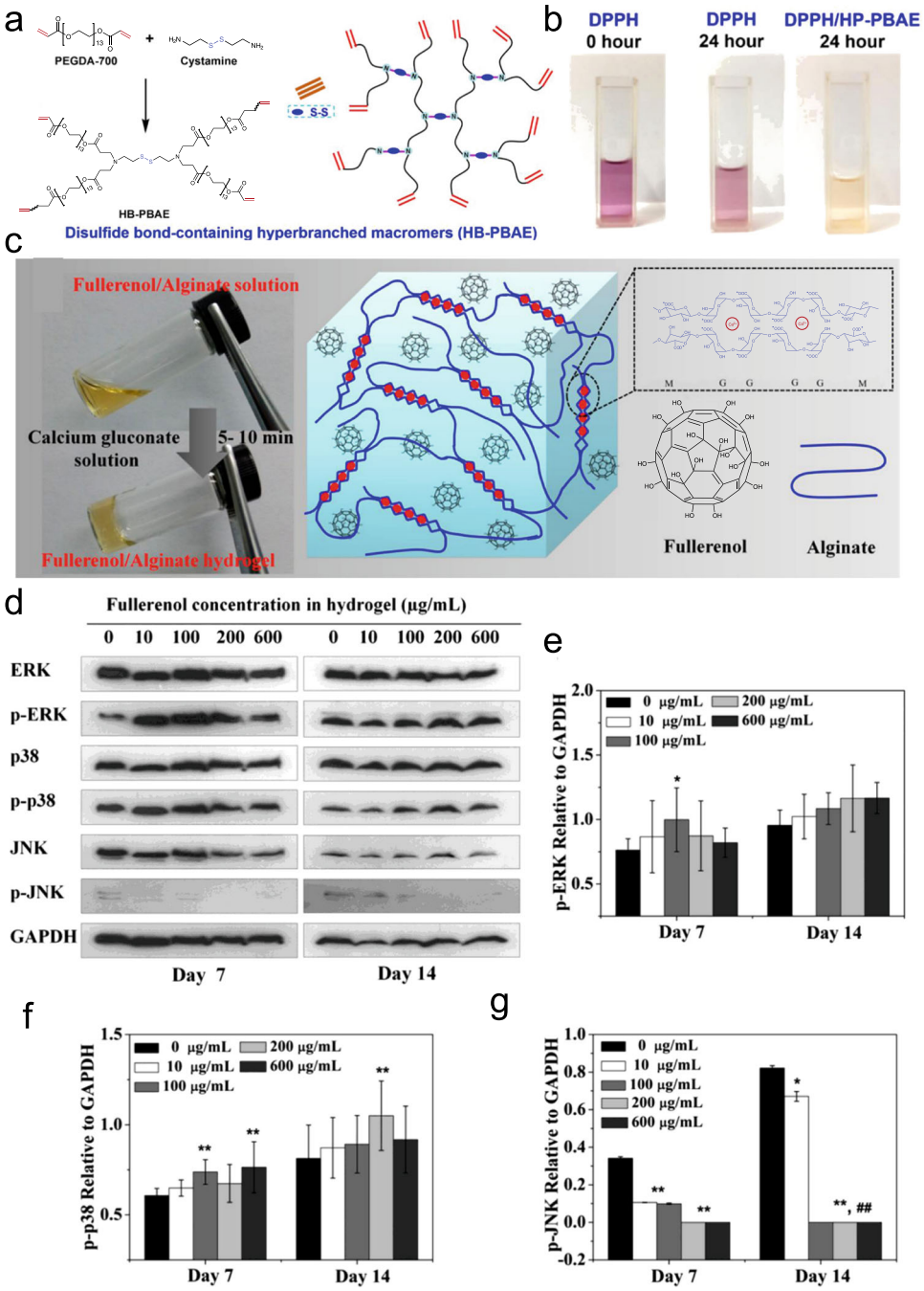

Fig. 3 ROS-scavenging hydrogels used for treating MI. a Synthesis of ROS-sensitive hyperbranched macromer (HB-PBAE). **b** Photograph of DPPH and DPPH/HB-PBAE solutions after 24 h. Copyright 2018, American Chemical Society (ref. [59]). **c** Formation and structure of fullerenol/alginate hydrogel. **d**-**g** Representative western blot assay and quantitative expression analysis of ERK, p-ERK, p38, p-p38, JNK, and p-JNK in BADSCs in the presence of H_2O_2. Copyright 2017, American Chemical Society (ref. [65]).

cardiomyocyte apoptosis under oxidative stress, and preserve the structure of the left ventricle, including retention of an overall small size and increased wall thickness. Additionally, Li et al.[63] developed an antioxidant chitosan chloride-glutathione (CSCl-GSH) hydrogel by coupling the antioxidant GSH to CSCl. The antioxidant capacity of this CSCl-GSH hydrogel could be controlled by adjusting the coupling amount of GSH. The results demonstrated that the CSCl-GSH hydrogel could effectively scavenge ROS, reduce excessive intracellular ROS, and support myocardial repair by reducing oxidative stress damage to cells.

ROS-scavenging hydrogels not only have the capacity to reduce oxidative damage of CMs in the infarcted myocardium but also improve the therapeutic effects of transplanted cells. Indeed, a ROS-scavenging chitosan hydrogel was used to deliver adipose-derived mesenchymal stem cells (ADSCs) to repair MI[64]. The results showed that this hydrogel improves the engraftment ratio of transplanted stem cells through ROS-scavenging. Similarly, Hao et al.[65] synthesized a stem cell carrier with antioxidative capacity by introducing fullerenol nanoparticles with antioxidant properties into alginate hydrogels (Fig. 3c). This fullerenol/alginate hydrogel effectively removes superoxide anions and hydroxyl radicals, activates the ERK and p38 pathways, inhibits the JNK pathway to suppress oxidative stress damage to stem cells (Fig. 3d-g), and improves stem cell viability in the ROS microenvironment. In vivo studies further demonstrated that this antioxidant hydrogel could effectively reduce ROS levels in the infarct area, improve the survival rate of transplanted stem cells, and facilitate cardiac functional recovery. Such ROS-scavenging hydrogels are anticipated to enhance the therapeutic efficiency of existing stem cell therapies.

Immunomodulatory hydrogels

The immune system makes a significant contribution to cardiac development, composition, and function. Immune cells infiltrate and remain in the heart at gestation[66]. However, shortly after MI, a series of internal changes in the myocardium, including the release of preformed granules from resident mast cells, inflammatory cytokines and chemokines from resident macrophages and CMs and hematopoietic growth factor from cardiac fibroblasts, as well as activation of endothelial cells, induces the recruitment of many neutrophils and monocytes to the infarct site, where they actively participate in the inflammatory cascade[67,68]. In the early stage of inflammation, monocytes are polarized into proinflammatory subtypes that secrete proinflammatory chemokines and are responsible for scavenging apoptotic cells and debris[69]. The inflammatory phase is replaced by the reparative phase in the following days, which manifests as reductions in inflammatory cytokines, growth factors, and chemokines[70]. In particular, macrophages gradually shift from a proinflammatory M1-type phenotype to an anti-inflammatory M2-type phenotype with various regeneration-promoting functions. In infarcted myocardium, the controlled recruitment and activation of monocytes and macrophages are necessary for tissue repair and angiogenesis to limit the formation of excessive scarring and fibrotic tissues; however, excessive and sustained inflammatory activation can lead to maladaptive healing and ventricular remodeling[28]. Therefore, regulating the inflammatory response, via immunomodulatory mechanisms, at the infarct site provides a protective effect on cardiac function.

Immunomodulation via mesenchymal stem cells (MSCs) plays an important role in the treatment of MI[71]. Studies have shown that MSCs regulate inflammation by inhibiting the expression of proinflammatory cytokines, such as tumor necrosis factor (TNF)-α, interleukin (IL)-6, and interferon (IFN)-γ, or by promoting the expression of anti-inflammatory cytokines, such as IL-10 and IL-12[71]. To improve the retention and survival rates of MSCs at the implanted site, Liu et al. encapsulated bone marrow-derived MSCs (BMSCs) in a chitosan hydrogel to treat MI[72]. The results confirmed that this hydrogel system could reduce inflammatory reactions in the infarct area by inhibiting the expression of proinflammatory factors (IL-6, TNF-α, IL-1b, IL-18, caspase-11, and caspase-1), protecting vascular endothelial cells and improving cardiac function. Similarly, in Shin's work[73], MSCs were encapsulated in alginate and subsequently loaded in poly (ethylene) glucose hydrate to treat myocardial ischemia/reperfusion. A new immunomodulatory mechanism mediated by MSCs was studied in this paper. That is, MSCs were found to regulate excessive inflammation and reduce innate immune cell infiltration and hydrogen peroxide formation by increasing adenosine bioavailability via the surface ecto-50-nucleotidase CD73.

Although many cell types are involved in tissue repair, macrophages exhibit critical regulatory activity throughout all stages of repair and fibrosis. In fact, increasing evidence shows that the balance between macrophage classical (M1) and altered (M2) activation governs the fate of tissue regeneration[74]. Therefore, polarizing macrophages toward the M2 phenotype has become a targeted approach to promote cardiac function recovery. In fact, Liu's team[75] synthesized a hydrogel with immunomodulatory properties that was composed of ECM from the spleen, the largest immune system in the body, with the spleen ECM playing an important role in immune function. This spleen-specific hydrogel enhances cardiac function by promoting the anti-inflammatory M2 polarization of macrophages. In addition, extracellular vesicles or immunomodulatory cytokines have been encapsulated into hydrogels to protect myocardial function by attenuating the inflammatory response in the infarct area by regulating macrophage polarization[28,76]. In a recent study, a hydrogel system (Gel@MSNs/miR-21-5p) with immunomodulatory and angiogenic functions was used for the first time to improve cardiac function after MI[77]. In this system, mesoporous silica nanoparticles (MSNs) were used as the carrier of miR-21-5p, which were crosslinked to an injectable hydrogel through formation of Schiff base bonds, which were broken in the acidic environment of the infarcted area, allowing for the release of MSNs/miRNA. MSNs may modulate the immune response via

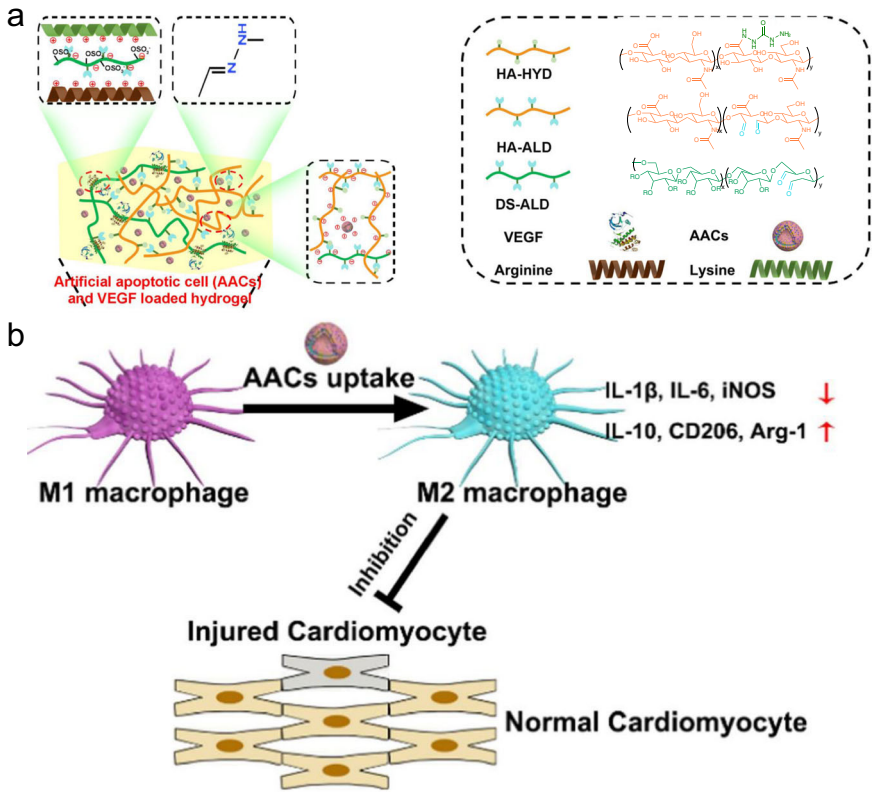

Fig. 4 Immunomodulatory hydrogels used for treating MI. a Schematic illustration of the formation of AAC/VEGF-loaded ECM-mimicking hydrogel. **b** Schematic diagram illustrating the immunomodulation of AACs to downregulate inflammatory factors to protect cardiomyocytes. Copyright 2021, Elsevier Science (ref. [78]).

downregulation of Toll-like receptor (TLR)2, which inhibits the activation of nuclear factor kappa B (NF-κB) signaling and subsequently decreases the release of proinflammatory cytokines (TNF-α, IL-1β, and IL-6). Moreover, miR-21-5p targets SPRY1, causing subsequent activation of vascular endothelial growth factor (VEGF)-induced extracellular signal-regulated kinase 1/2 (ERK)-mitogen-activated protein kinase (MAPK) signaling to promote angiogenesis and mature vessel formation. In a recent study by our group, an ECM-mimicking hydrogel system with immunomodulatory and angiogenic functions was established to treat MI (Fig. 4a)[78]. The hydrogel was synthesized through a Schiff reaction between hydrazide-hyaluronic acid (HA-HYD) and aldehyde-hyaluronic acid (HAALD) and aldehyde-dextran sulfate (DS-ALD). Then, artificial apoptotic cells (AACs) and VEGF were encapsulated into this injectable hydrogel. AACs are composed of the main components of the apoptotic cell membrane, including phosphatidylserine (PS), phosphatidylcholine (PC) and cholesterol. Because of the different electrostatic interactions between AACS, VEGF and hydrogel, the rapid release of AACS and the slow release of VEGF could be achieved. The results revealed that the released AACs could be internalized by macrophages and exert immune regulation via the promotion of M1 macrophage polarization to M2 macrophages (Fig. 4b), while VEGF promoted angiogenesis in the infarct area.

The effector molecules of the adaptive immune response can greatly promote the innate immune response. For example, antibodies can promote the phagocytic ability of phagocytes and the cytotoxicity of NK cells. Moreover, the cytokines secreted by T cells can promote the maturation, migration, and cytotoxic capacity of innate immune cells participating in the response. Hence, the repair function of adaptive immunity is gradually being studied and exploited by researchers to promote cardiac function after MI. For instance, Hofmann et al.[79] demonstrated that T lymphocytes, especially $CD4^+$ T cells, became activated and played an important role in wound healing after MI; moreover, reduced $CD4^+$ T-cell activation could cause the formation of collagenous scar tissue. This research group[80] further confirmed the functional role of $Foxp3^+$ $CD4^+$ regulatory T cells (T_{reg} cells) in wound healing after MI. They found that activation of Tregs could induce an M2-like macrophage phenotype and reduce proinflammatory responses within the healing myocardium. Moreover, Zacchigna et al.[81]

confirmed that Tregs could promote cardiomyocyte proliferation in a paracrine manner via the secretion of six factors (CST7, TNFSF11, IL33, FGL2, MATN2, and IGF2) by Tregs. Collectively, these studies demonstrated the complex interplay between adaptive (T cells) and innate (macrophages) immunity following MI while presenting a novel therapeutic modality for the treatment of patients with MI.

Conductive hydrogels

The myocardium is a tissue that contracts and relaxes in response to electrical impulses[82]. However, the formation of fibrous scar tissue in the infarcted area hinders the electrical conduction of the heart after MI, making the synchronous contraction between normal myocardial tissue and fibrous scar tissue abnormal, ultimately causing ventricular dysfunction. Conductive hydrogels act as a bridge to enhance the communication and electrical coupling between normal and damaged CMs, facilitating the resynchronization of cardiac contractions and improving cardiac function[83,84]. Therefore, conductive hydrogels are widely used in cardiac tissue engineering. The conductivity range of native myocardium varies from 10^{-4} to 10 S/cm[85], which can be used as reference values for preparing conductive hydrogels used in repairing cardiac tissue engineering after MI.

Conductive nanostructures and conductive polymers are generally used to form electron-conductive hydrogels and are applied in cardiac tissue engineering[86,87]. Navaei et al.[88] introduced gold nanorods (GNRs) into a methacryloyl gelatin (GelMA) solution to construct conductive hydrogels. The electrical conductivity of the hybrid hydrogel was adjusted to allow rhythmic contraction of the CMs when cultured on GelMA-GNR hydrogels. Similarly, Pok et al.[89] prepared a conductive hydrogel by dispersing carbon nanotubes into a hydrogel precursor solution by ultrasound. This hydrogel significantly improved the electrical coupling between CMs. In addition, a conductive polypyrrole (PPy)-chitosan hydrogel was synthesized and used for treating MI[90]. The results demonstrated that compared with a nonconductive hydrogel, the conductive hydrogel effectively enhanced Ca^{2+} signal conduction in neonatal rat CMs in vitro while decreasing the QRS interval and improving electrical pulse signal conduction and cardiac function after MI.

Recently, our research group also reported the application of a series of conductive hydrogels in treating MI. For example, graphene oxide (GO) was incorporated into a PEGDA700-melamine/thiol-modified HA (PEG-MEL/HA-SH) hydrogel[81]. The introduction of GO improves not only the conductivity but also the stability and antifatigue capacity of the hydrogels. Next, considering the metabolic toxicity of conductive particles, we developed new conductive systems. For example, tetraaniline (TA), as an excellent electroactive and biocompatible material, was combined with PEGDA to obtain a multiarmed conductive crosslinker tetraaniline-polyethylene glycol diacrylate (TA-PEG), which is capable of forming hydrogels (TA-PEG/HA-SH) with HA-SH through a Michael addition reaction[91]. The results suggest that the TA-PEG/HA-SH hydrogel has excellent conductivity, corresponding to that of myocardial tissue, which can be altered by adjusting the concentration of TA-PEG. In addition, unlike doping PPy into hydrogels, our group developed and synthesized new conductive hydrogels based on PPy[12,92]. The pyrrole monomer was coupled to a water-soluble hyperbranched macromolecule, and PPy was formed by in situ polymerization under the action of an oxidant, thus avoiding the inhomogeneity of directly mixing polypyrrole into hydrogels (Fig. 5a)[92]. Moreover, conductive PPy served as a crosslinking site, making the gel network and conductive system more stable and uniform. Furthermore, the conductive hydrogel patch maintained a relatively normal QRS interval (Fig. 5b) and effectively promoted electric pulse signal conduction and gap junction protein (Cx-43) expression in infarcted myocardium (Fig. 5c). In another study, we modified PPy with dopamine to enhance its hydrophilicity, allowing it to disperse evenly in the hydrogel precursor solution[12]. A homogeneous hydrogel network was prepared between dopamine-gelatin (GelDA) conjugates and dopamine-functionalized polypyrrole (DA-PPy) under Fe^{3+}-induced ionic coordination. This conductive hydrogel, as a cardiac patch, also improves electrical signal conduction in infarct myocardium. In a recent study, PPy-chitosan hydrogel (PPY-CHI) hydrogel was used to explore the function of conductive hydrogels in preventing heart failure[93]. The results demonstrated that conductive hydrogels could enhance electrical conductivity to synchronize cardiac contractions by reducing the electrical resistivity of the infarcted area, providing a theoretical basis for the application of conductive hydrogels in MI treatment.

Although electronic conductors can endow hydrogels with good conductivity and have achieved excellent therapeutic effects in the treatment of MI, the generation of heterogeneous networks is inevitable when embedded into hydrophilic hydrogels due to their hydrophobicity[94,95]. Therefore, ionic conductive hydrogels have been gradually applied for the treatment of MI. For instance, a conductive choline-based bioionic liquid (Bio-IL) integrated into a GelMA-based hydrogel promotes the adhesion, proliferation, and electromodulation of primary CMs in vitro[96]. Moreover, PAA, which exhibits electrical activity owing to the carboxyl groups on its side chain undergoing deprotonation into carboxylate ions in the media, was introduced into an oxidized alginate (OA)/gelatin (Geln) system to synthesize a novel hydrogel

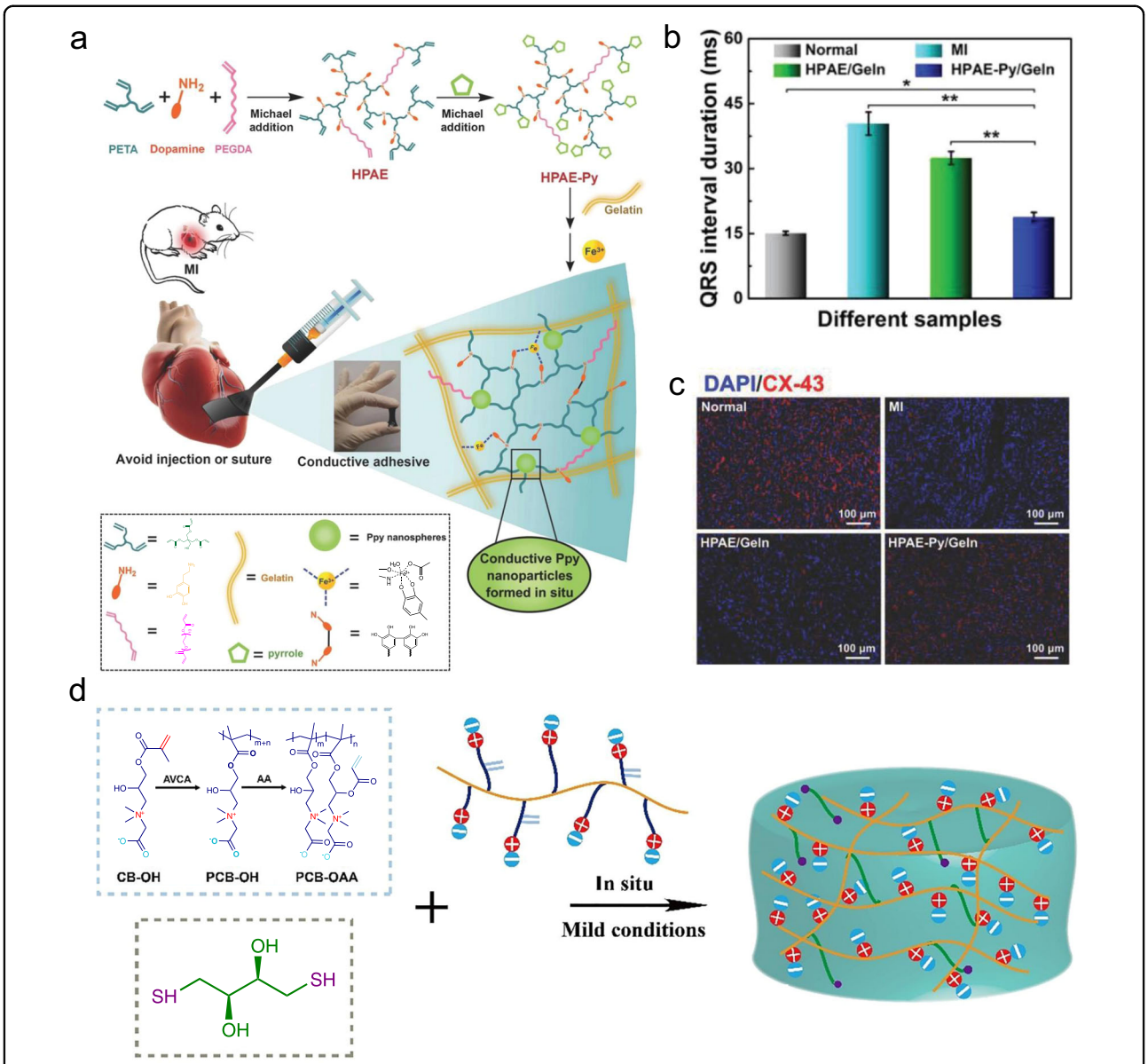

Fig. 5 Conductive hydrogels used for treating MI. a Schematic illustration of the formation of a conductive and adhesive hydrogel and its application by painting directly on the surface of MI hearts in SD rats. **b** QRS intervals determined by ECG. **c** Immunofluorescent staining images of Cx-43 protein expression in infarcted hearts after 4 weeks. Copyright 2018, Wiley & Sons Inc. (ref. [91]). **d** Schematic illustration of a conductive zwitterionic PCB-OAA hydrogel. Copyright 2021, Elsevier Science (ref.[97]).

(POG) with excellent conductivity and self-healing properties[85]. The conductivity of the hydrogel could be adjusted by changing the PAA concentration ($35.36 \pm 7.72 \times 10^{-3}$ S/cm was achieved when the PAA content was 16.6 mg/ml). The POG1 hydrogel also participates in effective crosstalk with CMs through electrical signaling and promotes the resynchronization of CMs. In vivo studies have demonstrated that POG1 hydrogel could significantly reduce left ventricular remodeling and restore myocardial function. Our research group recently synthesized an ionic conductive zwitterionic (PCB-OAA) hydrogel. In this study, zwitterionic PCB-OH polymers were prepared by thermally initiated polymerization of a CB-OH monomer, and then macromonomer PCB-OAA was synthesized by an acylation reaction between PCB-OA and acrylic anhydride (Fig. 5d)[97]. The PCB-OAA hydrogel was prepared by simply mixing PCB-OAA and DTT via a Michael addition reaction. The cation-anion ion pair on the side chain affords the PCB-OAA hydrogel excellent conductivity similar to that of the native myocardium. Moreover, it can improve the expression of Cx-43 when injected into infarcted areas after MI. Hence, the

construction of conductive hydrogels for cardiac repair is of great significance, as they facilitate improved intercellular communication.

Proangiogenic hydrogels

Angiogenesis is essential in the process of embryo growth and for physiological repair throughout life[98]. During MI, an insufficient blood supply to the myocardium represents an important cause of myocardial cell death and left ventricle pathological remodeling; thus, the formation of new blood vessels is of great significance after MI[99]. In addition, the formation of new blood vessels can restore the blood and nutrient supply to ischemic myocardium[100].

Nitric oxide (NO) is an endogenous bioactive factor and, as a signal molecule, can mediate the regulation of many pathways, including those associated with the circulatory system and cardiac protection[101,102]. In the treatment of MI, exogenous NO can stimulate the formation of blood vessels by promoting the expression of proangiogenic cytokines, reducing the unadaptable remodeling of the left ventricle and improving myocardial function[103]. Therefore, many researchers have developed NO production hydrogels (including exogenous NO supplementation and endogenous NO generation) for treating MI.

The β-galactose-caged NO donor is covalently bound to naphthalene-conjugated short peptide (NapFF) to form hydrogels (NapFF-NO) through the self-assembly of peptide chains and release NO in response to β-galactosidase (Fig. 6a)[104]. In vitro experiments showed that the NapFF-NO hydrogel could activate VEGF/VEGFR2 pathways by releasing NO to promote the expression of vascular-related factors, endothelial cell migration, and angiogenesis (Fig. 6b). Meanwhile, in vivo, NapFF-NO hydrogels have been shown to release NO continuously in the myocardium, reduce left ventricular unadaptable remodeling, and increase the vascularization of infarcted myocardial tissue. Similarly, Ou et al[105]. introduced NO donors into hydrogels to improve cardiac function after MI. They synthesized two types of peptide derivatives, namely, Compound 1 containing curcumin (anti-inflammatory, antioxidation, and antiapoptotic effects) and Compound 2 containing an NO donor. When the two components were mixed with a suitable amount of GSH, they formed supramolecular hydrogels, which could continue to release curcumin for over 24 h and release NO continuously under the catalysis of β-galactosidase. The results demonstrated that NO could inhibit inflammation after MI by regulating the expression of TGF-β1 and promoting the regeneration of blood vessels, thus improving damaged myocardial tissue. In vivo results showed that the combination of curcumin and NO could maintain the geometric structure of the left ventricle and reduce collagen deposition and ventricular remodeling. The excessive ROS produced after MI could rapidly metabolize NO to form peroxynitrite, which further induces nitrous stress and tissue damage and reduces NO bioavailability. In view of this, Nagasaki et al.[106] synthesized a hydrogel that simultaneously releases NO and scavenges ROS. L-arginine, which could react with iNOS enzymatically to release NO, was introduced to the hydrogel, along with the PMNT-PEGPMNT polymer, which could eliminate ROS and protect against endogenous NO. The results demonstrated that the hydrogel continually releases NO and improves its bioavailability in the infarcted area. Unlike using NO donors, Wang et al.[91] incorporated DNA-eNOs into an injectable hydrogel, which could promote the release of NO through the efficient and controllable expression of eNOs in MI. They demonstrated that the hydrogel transports the eNOs gene to the MI area and promotes its transfection and expression. Meanwhile, the expression of eNOs promotes the release of NO from endothelial cells, thus inducing neovascularization, improving the local blood supply to the MI area and promoting the recovery of cardiac function.

In addition to angiogenesis through the exogenous supply of NO, proteins related to angiogenesis have also been encapsulated into hydrogels to promote angiogenesis in infarcted myocardium. For example, VEGF-A was loaded on a PEGylated fibrinogen hydrogel to improve arteriogenesis in the infarcted myocardium[107]. Enhanced angiogenesis is more effectively achieved via the delivery of multiple growth factors than a single factor. Thus, two vascular-related growth factors, VEGF and platelet-derived growth factor (PDGF), have been used in the treatment of MI[99]. VEGF is an important factor for angiogenesis, and PDGF can recruit mural cells to cover neovessels and provide stability after luminal formation. Since the affinity of PDGF to heparin is weaker than that of VEGF, PDGF is easier to release from the heparin-based coacervate. Therefore, to achieve the sequential release of VEGF and PDGF, VEGF was embedded in a fibrin gel, and PDGF was embedded in a heparin-based coacervate, which was then distributed in the above fibrin gel (Fig. 6c, d). This system was found to rapidly release VEGF to promote angiogenesis and stabilize the vasculature through the subsequent release of PDGF. The sequential delivery group showed more neovascularization and mature vessels, improved cardiac function, and reduced infarct area than the other groups (Fig. 6e). Additionally, Coulombe et al.[108] used three proteins to promote vascular regeneration: VEGF, bFGF, and sonic hedgehog (Shh). Among those, VEGF and bFGF have been included in angiogenesis therapies, as they are key factors in angiogenesis during embryonic development and

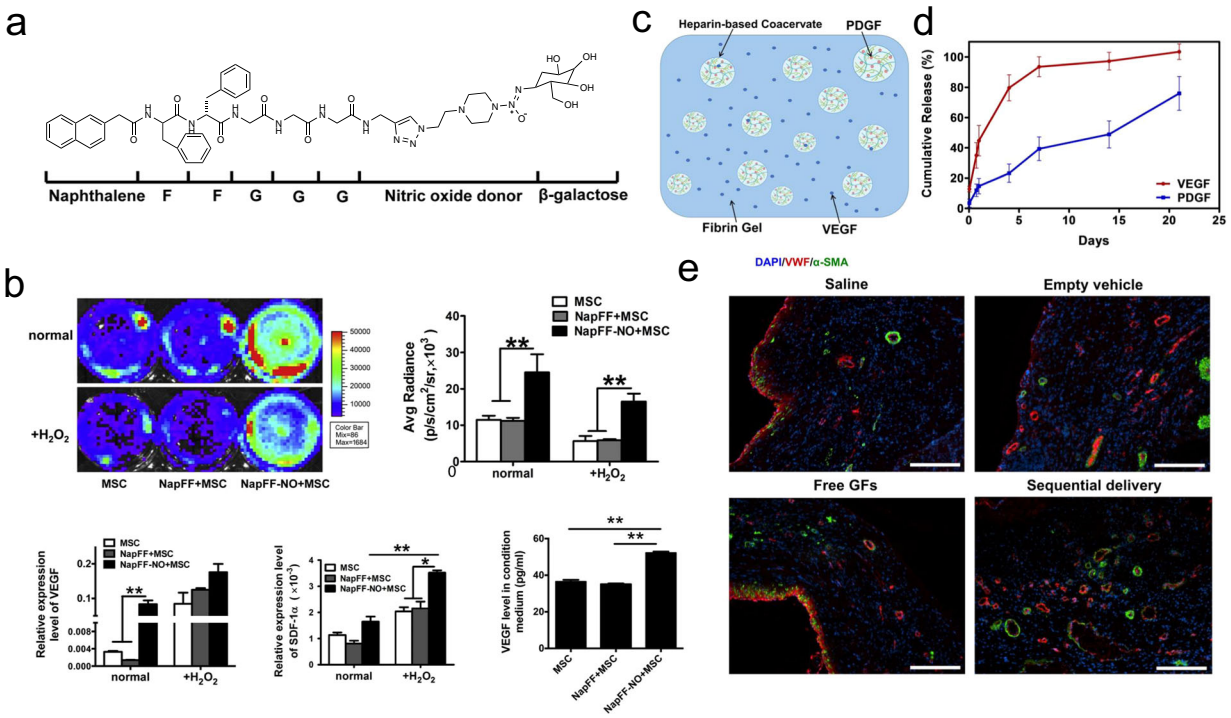

Fig. 6 Proangiogenic hydrogels used for treating MI. a Structural formula of NapFF-NO hydrogel. **b** NapFF-NO hydrogel-promoted AD-MSC paracrine secretion of angiogenic cytokines. Copyright 2015, Elsevier Science (ref. [99]). **c** Schematic illustration of the sequential release of VEGF and PDGF. **d** Release curve of VEGF and PDGF from the hydrogel. **e** Immunofluorescence analysis of VWF (red) and α-SMA (green) to reflect the level of neovascularization. Copyright 2015, Elsevier Science (ref. [104]).

demonstrate synergistic effects in adult vascular reconstruction, while Shh is a morphogenetic agent activated in the early embryo to promote the development of three-dimensional tissue and the stability of neovascularization. These proteins were loaded in alginate microspheres and incorporated in a collagen-based hydrogel. The effects of VEGF and bFGF in the two-dimensional vascularization experiment were superimposed, and Shh further enhanced the growth of blood vessels in the three-dimensional modified aortic ring vascularization experiment, which showed that the three angiogenic proteins together promoted angiogenesis more effectively than any single protein. In vivo, the number of blood vessels in the infarct area of the animals treated with a combination of CMs and angiogenic factors increased by 49.8% compared with that in the untreated animals, and heart function was improved. Thus, vascular regeneration is an important process in myocardial repair. Regardless of the method selected to promote the formation of vessels in the infarct area, they represent potential future treatment options for MI.

3D-printed hydrogels

3D printing technology is widely used in cardiac tissue engineering, as it can be customized to create the complex structures of myocardial tissues while integrating materials and cells[44,45]. Lee et al.[109] developed a new bioink using gelatin, GelMA, and methacryloyl-substituted recombinant human collagen (MeTro) (Fig. 7a). Meanwhile, lithium phenyl-2,4,6-trimethylbenzoylphosphinate (LAP) was used as the photoinitiator to generate bioprinted structures crosslinked under visible light, thereby eliminating the effect of ultraviolet radiation on cells (Fig. 7b). The introduction of MeTro enhanced the resilience of composite hydrogels, which could be modified to achieve similar soft tissue mechanics and support cell adhesion and proliferation. For the 3D printing process, cardiac fibroblasts (CFs)/CMs and human umbilical vein endothelial cells (HUVECs) were loaded in GelMA bioink to represent parenchymal cardiac tissue, and HUVECs were loaded in MeTro/GelMA bioink to form vessels (Fig. 7c-f). The printed hydrogel structure shows the function of the endothelial barrier and the spontaneous beating of myocardial cells, which are important functions of heart tissue in vivo. Liu et al.[44] mixed neonatal rat ventricular myocytes (NMVCMs) with hydrogel precursor solutions and constructed a 3D hydrogel scaffold simulating the myocardial structure via microscale continuous optical printing (μCOP). This hydrogel scaffold consists of three types of hydrogels, namely, a basal layer, 2% HAGM/2%

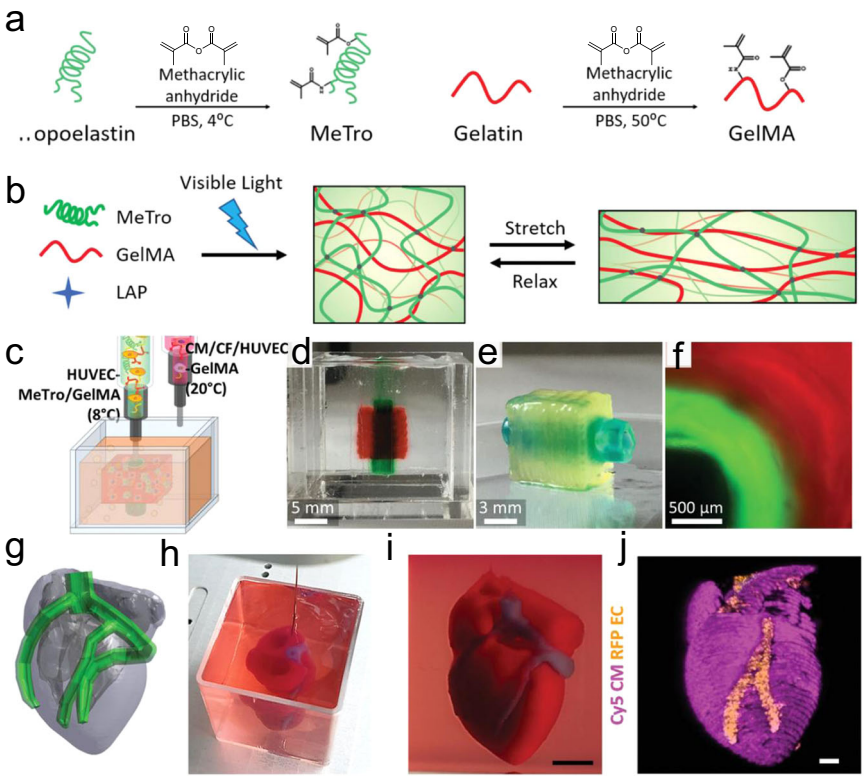

Fig. 7 3D-printed hydrogels used for cardiac tissue engineering. a, **b** Synthesis process of the GelMA/MeTro composite hydrogel. **c** Schematic describing the 3D bioprinting of vascularized cardiac constructs with HUVEC-laden MeTro/GelMA bioink and CM/CF/HUVEC-laden GelMA bioink. **d**-**f** Construction process of vascularized cardiac tissue. Green and red food colors were used to distinguish the MeTro/GelMA and GelMA bioinks, respectively. Copyright 2020, Wiley & Sons Inc. (ref. [109]). **g** Human heart CAD model. **h**, **i** A printed heart within a support bath. **j** 3D confocal image of the printed heart (CMs in pink, ECs in orange). Copyright 2019, Wiley & Sons Inc. (ref. [110]).

PEGDA; cantilevers, 15% GelMA; and a parallel line pattern, 5% GelMA. CMs encapsulated in this 3D hydrogel scaffold could align with the engineered microarchitecture and display the morphology and myofibril alignment phenotypes of the myocardium in vivo. In addition to 3D printing myocardial tissues, the whole heart has been generated in this manner. To achieve this, hydrogels with extracellular matrix as a bioink are used[110]. Endothelial cells and cardiac myocytes are combined with hydrogel ink to form cardiac parenchyma tissue and vascular structure, respectively (Fig. 7g-j). Similarly, Lee et al.[45] proposed a method for 3D bioprinting collagen using freeform reversible embossing of suspended hydrogels (FRESH) to design human heart components at different scales, from capillaries to entire organs. Following encapsulation of CMs in the collagen, the resulting 3D-printed cardiac ventricles showed synchronized contractions, oriented action potential propagation, and a 14% thickened wall during peak systole. Although 3D printing of cardiac scaffolds or intact hearts can achieve certain functions in vitro, its mechanical properties are far from those of natural myocardial tissue.

Other hydrogels

In addition to NO, gaseous signaling molecules, such as CO and H_2S, have anti-inflammatory, antiapoptotic and cell-protective roles in cardiovascular diseases[111,112]. Therefore, CO- or H_2S-releasing hydrogels have also been used to treat MI. For example, Kim et al.[113] developed a CO-releasing peptide hydrogel. First, tricarbonylchloro (glycinato)ruthenium (II) (CORM-3, Ru(CO)3Cl(glycinate)), which could process a water-gas shift under physiological conditions, was incorporated into diphenylalanine (FF)-peptide; thereafter, the hydrogel was formed by coassembling the CORM-3-attached FF-peptide and fluorenylmethoxycarbonyl (Fmoc)-FF. The results demonstrated that the CO-releasing hydrogel could reduce cardiomyocyte apoptosis under oxidative stress conditions. Furthermore, our research group synthesized an H_2S-releasing hydrogel[114], in which the H_2S donor 2-aminopyridine-5-thiocarboxamide was coupled to oxidized alginate by a Schiff base reaction. The hydrogel was shown to release H_2S under L-cysteine stimulation and exhibited anti-inflammatory and angiogenic functions in the treatment of MI. In another study[115], calcium oxide was loaded on the

cardiac patch, and oxygen was slowly produced following contact with the moist myocardium, which could improve the hypoxic conditions of infarcted areas and increase the survival rate of CMs. The use of gaseous signaling molecules to improve the cardiac microenvironment is also a potential method for the treatment of MI.

Conclusions and future outlook

This review briefly introduces the variations within the myocardial microenvironment after MI and the application of functional hydrogels in treating MI. Since the myocardial microenvironment is highly complex following MI, functional hydrogels are currently designed to address only one or two aspects of this system. Therefore, it is expected that more composite functional hydrogels will be developed in the future to allow complete healing of the myocardium after injury. In addition to functional matching, the mechanical properties of hydrogels must also mimic those of natural myocardial tissue, with the materials used already approved for medical use. The three-dimensional network structure of hydrogels can facilitate the transportation of nutrients, but this transportation process is mainly achieved by diffusion. Dense hydrogel networks limit the transportation of nutrients and tissue ingrowth. The effectiveness of cell therapy and tissue regeneration are closely related to the porosity of biomaterials. Therefore, porous hydrogels are promising cardiac patches. Moreover, to date, the therapeutic effect of hydrogels on MI has only been verified in small animal models; therefore, it will also be necessary to perform large animal and clinical studies to further confirm the observed effects and to detect any potential adverse events. Additionally, the studies that have examined the therapeutic potential of hydrogels have only done so over a maximum time period of 1 month, which is not sufficient to detect any long-term effects. Thus, longer-duration studies are warranted to evaluate the effects of cardiac function following hydrogel degradation. Moreover, exploring a feasible minimally invasive therapeutic to replace the current thoracotomy will be required to alleviate injury following MI in the future.

Acknowledgements
This work was supported by the National Natural Science Foundation of China (Grant No. 31771030) and the National Key Research and Development Program of China (Grant No. 2016YFC1101301).

Author contributions
T.W. reviewed the literature and composed a draft manuscript. W.L. edited the manuscript and supervised the work.

Competing interests
The authors declare no competing interests.

Received: 1 July 2021 Revised: 16 August 2021 Accepted: 23 August 2021.
Published online: 18 February 2022

References

1. Shi, H. P. et al. Microneedle-mediated gene delivery for the treatment of ischemic myocardial disease. *Sci. Adv.* **6**, eaaz3621 (2020).
2. Wu, Y. et al. Release of VEGF and BMP9 from injectable alginate based composite hydrogel for treatment of MI. *Bioact. Mater.* **6**, 520–528 (2021).
3. Lin, X. et al. A viscoelastic adhesive epicardial patch for treating MI. *Nat. Biomed. Eng.* **3**, 632–643 (2019).
4. Fiedler, J. & Thum, T. MicroRNAs in MI. *Arterioscler Thromb. Vasc. Biol.* **33**, 201–205 (2013).
5. Sepantafar, M. et al. Stem cells and injectable hydrogels: synergistic therapeutics in myocardial repair. *Biotechnol. Adv.* **34**, 362–379 (2016).
6. Pena, B. et al. Injectable hydrogels for cardiac tissue engineering. *Macromol. Biosci.* **18**, 1800079 (2018).
7. Heallen, T. R. & Martin, J. F. Heart repair via cardiomyocyte-secreted vesicles. *Nat. Biomed. Eng.* **2**, 271–272 (2018).
8. Hashimoto, H., Olson, E. N. & Bassel-Duby, R. Therapeutic approaches for cardiac regeneration and repair. *Nat. Rev. Cardiol.* **15**, 585–600 (2018).
9. Marban, E. A mechanistic roadmap for the clinical application of cardiac cell therapies. *Nat. Biomed. Eng.* **2**, 353–361 (2018).
10. Zhang, Y. et al. A collagen hydrogel loaded with HDAC7-derived peptide promotes the regeneration of infarcted myocardium with functional improvement in a rodent mode. *Acta Biomater.* **86**, 223–234 (2019).
11. Li, H. K. et al. Folic acid-derived hydrogel enhances the survival and promotes therapeutic efficacy of iPS cells for acute MI. *ACS Appl. Mater. Interfaces* **10**, 24459–24468 (2018).
12. Wu, T. L. et al. Coadministration of an adhesive conductive hydrogel patch and an injectable hydrogel to treat MI. *ACS Appl. Mater. Interfaces* **12**, 2039–2048 (2020).
13. Jackman, C. P. et al. Engineered cardiac tissue patch maintains structural and electrical properties after epicardial implantation. *Biomaterials* **159**, 48–58 (2018).
14. Pedron, S. et al. Stimuli responsive delivery vehicles for cardiac microtissue transplantation. *Adv. Funct. Mater.* **21**, 1624–1630 (2011).
15. Peña, B. et al. Injectable hydrogels for cardiac tissue engineering. *Macromol. Biosci.* **18**, 1800079 (2018).
16. Camci-Unal, G., Annabi, N., Dokmeci, M. R., Liao, R. & Khademhosseini, A. Hydrogels for cardiac tissue engineering. *NPG Asia. Mater.* **6**, e99 (2014).
17. Nguyen, M. M. et al. Enzyme-responsive nanoparticles for targeted accumulation and prolonged retention in heart tissue after MI. *Adv. Mater.* **27**, 5547–5552 (2015).
18. Kampourides, N. et al. Usefulness of matrix metalloproteinase-9 plasma levels to identify patients with preserved left ventricular systolic function after acute MI who could benefit from eplerenone. *Am. J. Cardiol.* **110**, 1085–1091 (2012).
19. Zhang, Y. et al. Biomimetic design of mitochondria-targeted hybrid nanozymes as superoxide scavengers. *Adv. Mater.* **33**, 2006570 (2021).
20. Yao, Y. J. et al. ROS-responsive polyurethane fibrous patches loaded with methylprednisolone (MP) for restoring structures and functions of infarcted myocardium in vivo. *Biomaterials* **232**, 119726 (2020).
21. McMahan, S. et al. Current advances in biodegradable synthetic polymer based cardiac patches. *J. Biomed. Mater. Res.* **108**, 972–983 (2020).
22. Li, Y. et al. Injectable hydrogel with MSNs/microRNA-21-5p delivery enables both immunomodification and enhanced angiogenesis for MI therapy in pigs. *Sci. Adv.* **7**, eabd6740 (2021).
23. Purcell, B. P. et al. Delivery of a matrix metalloproteinase-responsive hydrogel releasing TIMP-3 after MI: effects on left ventricular remodeling. *Am. J. Physiol. Heart Circ. Physiol.* **315**, H814–H825 (2018).
24. Creemers, E. E. J. M., Cleutjens, J. P. M., Smits, J. F. M. & Daemen, M. J. A. P. Matrix metalloproteinase inhibition after MI-A new approach to prevent heart failure? *Circ. Res.* **89**, 201–210 (2001).
25. Wang, K. F. et al. Usefulness of plasma matrix metalloproteinase-9 level in predicting future coronary revascularization in patients after acute MI. *Coron. Artery Dis.* **24**, 23–28 (2013).

26. Sun, Y. Myocardial repair/remodelling following infarction: roles of local factors. *Cardiovasc. Res.* **81**, 482–490 (2009).
27. Spaulding, K. A. et al. Myocardial injection of a thermoresponsive hydrogel with reactive oxygen species scavenger properties improves border zone contractility. *J. Biomed. Mater. Res. A* **108**, 1736–1746 (2020).
28. Bloise, N. et al. Engineering immunomodulatory biomaterials for regenerating the infarcted myocardium. *Front. Bioeng. Biotech.* **8**, 292 (2020).
29. Zhao, G. X. et al. Anisotropic conductive reduced graphene oxide/silk matrices promote post-infarction myocardial function by restoring electrical integrity. *Acta Biomater.* https://doi.org/10.1016/j.actbio.2021.03.073 (2021).
30. Song, C. et al. An injectable conductive three-dimensional elastic network by tangled surgical-suture spring for heart repair. *ACS Nano* **13**, 14122–14137 (2019).
31. Wang, L. L. et al. Sustained miRNA delivery from an injectable hydrogel promotes cardiomyocyte proliferation and functional regeneration after ischaemic injury. *Nat. Biomed. Eng.* **1**, 983–992 (2017).
32. Wall, S. T., Walker, J. C., Healy, K. E., Ratcliffe, M. B. & Guccione, J. M. Theoretical impact of the injection of material into the myocardium. *Circulation* **114**, 2627–2635 (2006).
33. Zhu, Y., Matsumura, Y. & Wagner, W. R. Ventricular wall biomaterial injection therapy after MI: advances in material design, mechanistic insight and early clinical experiences. *Biomaterials* **129**, 37–53 (2017).
34. Park, S. J. et al. Dual stem cell therapy synergistically improves cardiac function and vascular regeneration following MI. *Nat. Commun.* **10**, 3123 (2019).
35. Huang, K. et al. An off-the-shelf artificial cardiac patch improves cardiac repair after MI in rats and pigs. *Sci. Transl. Med.* **12**, eaat9683 (2020).
36. Gustafson, J. A. et al. Synthesis and characterization of a matrix-metalloproteinase responsive silk-elastinlike protein polymer. *Biomacromolecules* **14**, 618–625 (2013).
37. Fonseca, K. B. et al. Enzymatic, physicochemical and biological properties of MMP-sensitive alginate hydrogels. *Soft Matter* **9**, 3283–3292 (2013).
38. Martin, J. R., Patil, P., Yu, F., Gupta, M. K. & Duvall, C. L. Enhanced stem cell retention and antioxidative protection with injectable, ROS-degradable PEG hydrogels. *Biomaterials* **263**, 120377 (2021).
39. Cheng, H. et al. Sprayable hydrogel dressing accelerates wound healing with combined reactive oxygen species-scavenging and antibacterial abilities. *Acta Biomater.* **124**, 219–232 (2021).
40. Zhou, J. et al. Injectable OPF/graphene oxide hydrogels provide mechanical support and enhance cell electrical signaling after implantation into myocardial infarct. *Theranostics* **8**, 3317–3330 (2018).
41. Kim, D. H. et al. Guided three-dimensional growth of functional cardiomyocytes on polyethylene glycol nanostructures. *Langmuir* **22**, 5419–5426 (2006).
42. Madden, L. R. et al. Proangiogenic scaffolds as functional templates for cardiac tissue engineering. *Proc. Natl Acad. Sci. USA* **107**, 15211–15216 (2010).
43. Soler-Botija, C., Galvez-Monton, C., Prat-Vidal, C., Roura, S. & Bayes-Genis, A. Myocardial bioprosthesis: mimicking nature. *Drug. Future* **38**, 475–484 (2013).
44. Liu, J. et al. Direct 3D bioprinting of cardiac micro-tissues mimicking native myocardium. *Biomaterials* **256**, 120204 (2020).
45. Lee, A. et al. 3D bioprinting of collagen to rebuild components of the human heart. *Science* **365**, 482–487 (2019).
46. Maral, S. et al. Matrix metalloproteinases 2 and 9 polymorphism in patients with myeloproliferative diseases. *Medicine* **94**, e732 (2015).
47. West, J. B., Watson, R. R. & Fu, Z. X. The honeycomb-like structure of the bird lung allows a uniquely thin blood-gas barrier. *Resp. Physiol. Neurobi.* **152**, 115–118 (2006).
48. Noujaim, D., van Golen, C. M., van Golen, K. L., Grauman, A. & Feldman, E. L. N-Myc and Bcl-2 coexpression induces MMP-2 secretion and activation in human neuroblastoma cells. *Oncogene* **21**, 4549–4557 (2002).
49. Wada, C. K. et al. Phenoxyphenyl sulfone N-formylhydroxylamines (retrohydroxamates) as potent, selective, orally bioavailable matrix metalloproteinase inhibitors. *J. Med. Chem.* **45**, 219–232 (2002).
50. Michaelides, M. R. & Curtin, M. L. Recent advances in matrix metalloproteinase inhibitor research. *Curr. Pharm. Des.* **5**, 787–819 (1999).
51. Eckhouse, S. R. et al. Local hydrogel release of recombinant TIMP-3 attenuates adverse left ventricular remodeling after experimental MI. *Sci. Transl. Med.* **6**, 223ra21 (2014).
52. Zavadzkas, J. A. et al. Targeted overexpression of tissue inhibitor of matrix metalloproteinase-4 modifies post-MI remodeling in mice. *Circ. Res.* **114**, 1435–1445 (2014).
53. Carlini, A. S. et al. Enzyme-responsive progelator cyclic peptides for minimally invasive delivery to the heart post-myocardial infarction. *Nat. Commun.* **10**, 1735 (2019).
54. Fan, Z. B. et al. Sustained release of a peptide-based matrix metalloproteinase-2 inhibitor to attenuate adverse cardiac remodeling and improve cardiac function following MI. *Biomacromolecules* **18**, 2820–2829 (2017).
55. Purcell, B. P. et al. Injectable and bioresponsive hydrogels for on-demand matrix metalloproteinase inhibition. *Nat. Mater.* **13**, 653–661 (2014).
56. Fan, C. X. et al. Myocardial-infarction-responsive smart hydrogels targeting matrix metalloproteinase for on-demand growth factor delivery. *Adv. Mater.* **31**, 1902900 (2019).
57. Xu, Q., He, C., Xiao, C. & Chen, X. Reactive oxygen species (Ros) responsive polymers for biomedical applications. *Macromol. Biosci.* **16**, 635–646 (2016).
58. Huo, M., Yuan, J., Tao, L. & Wei, Y. Redox-responsive polymers for drug delivery: from molecular design to applications. *Polym. Chem.* **5**, 1519–1528 (2014).
59. Wang, W. et al. Rebuilding postinfarcted cardiac functions by injecting TIIA@ PDA nanoparticle-cross-linked ROS-sensitive hydrogels. *ACS Appl. Mater. Interfaces* **11**, 2880–2890 (2018).
60. Han, X. X. et al. "Ferrero-like" nanoparticles knotted injectable hydrogels to initially scavenge ROS and lastingly promote vascularization in infarcted hearts. *Sci. China Tech. Sci.* **63**, 2435–2448 (2020).
61. Ding, J. et al. A reactive oxygen species scavenging and O_2 generating injectable hydrogel for MI treatment in vivo. *Small* **16**, 2005038 (2020).
62. Zhu, Y. et al. Reactive oxygen species scavenging with a biodegradable, thermally responsive hydrogel compatible with soft tissue injection. *Biomaterials* **177**, 98e112 (2018).
63. Li, J. J. et al. A chitosaneglutathione based injectable hydrogel for suppression of oxidative stress damage in cardiomyocytes. *Biomaterials* **34**, 9071e9081 (2013).
64. Liu, Z. Q. et al. The influence of chitosan hydrogel on stem cell engraftment, survival and homing in the ischemic myocardial microenvironment. *Biomaterials* **33**, 3093e3106 (2012).
65. Hao, T. et al. Injectable fullerenol/alginate hydrogel for suppression of oxidative stress damage in brown adipose-derived stem cells and cardiac repair. *ACS Nano* **11**, 5474–5488 (2017).
66. Swirski, F. K. & Nahrendorf, M. Cardioimmunology: the immune system in cardiac homeostasis and disease. *Nat. Rev. Immunol.* **18**, 733–744 (2018).
67. Frangogiannis, N. G. et al. Resident cardiac mast cells degranulate and release preformed TNF-alpha, initiating the cytokine cascade in experimental canine myocardial ischemia/reperfusion. *Circulation* **98**, 699–710 (1998).
68. Anzai, A. et al. The infarcted myocardium solicits GM-CSF for the detrimental oversupply of inflammatory leukocytes. *J. Exp. Med.* **214**, 3293–3310 (2017).
69. Nikolaos, G. F. The immune system and the remodeling infarcted heart: cell biological insights and therapeutic opportunities. *J. Cardiovasc. Pharmacol.* **63**, 83–84 (2014).
70. Kobara, M. et al. Antibody against interleukin-6 receptor attenuates left ventricular remodelling after myocardial infarction in mice. *Cardiovasc. Res.* **87**, 424–430 (2010).
71. Marta, M. T. et al. Local administration of porcine immunomodulatory, chemotactic and angiogenic extracellular vesicles using engineered cardiac scaffolds for myocardial infarction. *Bioact. Mater.* **6**, 3314–3327 (2021).
72. Liu, Y. et al. Chitosan hydrogel enhances the therapeutic efficacy of bone marrow-derived mesenchymal stem cells for myocardial infarction by alleviating vascular endothelial cell pyroptosis. *J. Cardiovasc. Pharmacol.* **75**, 75–83 (2020).
73. Shin, E. Y. et al. Adenosine production by biomaterial-supported mesenchymal stromal cells reduces the innate inflammatory response in myocardial ischemia/reperfusion injury. *J. Am. Heart Assoc.* **7**, e006949 (2018).
74. Duan, Y. Y. et al. Unsaturated polyurethane films grafted with enantiomeric polylysine promotes macrophage polarization to a M2 phenotype through PI3K/Akt1/mTOR axis. *Biomaterials* **246**, 120012 (2020).
75. Liu, G. et al. Enhancement of cardiac function with spleen-specific hydrogel via improving the immune microenvironment after myocardial infarction. *J. Biomater. Tiss. Eng.* **7**, 458–468 (2017).
76. Lv, K. Q. et al. Incorporation of small extracellular vesicles in sodium alginate hydrogel as a novel therapeutic strategy for myocardial infarction. *Theranostics* **9**, 7403–7416 (2019).

77. Li, Y. et al. Injectable hydrogel with MSNs/microRNA-21-5p delivery enables both immunomodification and enhanced angiogenesis for myocardial infarction therapy in pigs. *Sci. Adv.* **7**, eabd6740 (2021).
78. Zhang, X. P. et al. Artificial apoptotic cells/VEGF-loaded injectable hydrogel united with immunomodification and revascularization functions to reduce cardiac remodeling after myocardial infarction. *Nano Today* **39**, 101227 (2021).
79. Hofmann, U. et al. Activation of $CD4^+$ T lymphocytes improves wound healing and survival after experimental myocardial infarction in mice. *Circulation* **125**, 1652–U146 (2012).
80. Weirather, J. et al. $Foxp3^+$ $CD4^+$ T cells improve healing after myocardial infarction by modulating monocyte/macrophage differentiation. *Circ. Res.* **115**, 55–67 (2014).
81. Zacchigna, S. et al. Paracrine effect of regulatory T cells promotes cardiomyocyte proliferation during pregnancy and after myocardial infarction. *Nat. Commun.* **9**, 2432 (2018).
82. Bao, R. et al. A π-π conjugation-containing soft and conductive injectable polymer hydrogel highly efficiently rebuilds cardiac function after MI. *Biomaterials* **122**, 63–71 (2017).
83. Wang, L. L. et al. Mussel-inspired conductive cryogel as cardiac tissue patch to repair MI by migration of conductive nanoparticles. *Adv. Funct. Mater.* **26**, 4293–4305 (2016).
84. Hsiao, C. W. et al. Electrical coupling of isolated cardiomyocyte clusters grown on aligned conductive nanofibrous meshes for their synchronized beating. *Biomaterials* **34**, 1063–1072 (2013).
85. Song, X. P. et al. A tunable self-healing ionic hydrogel with microscopic homogeneous conductivity as a cardiac patch for MI repair. *Biomaterials* **273**, 120811 (2021).
86. Qazi, T. H., Rai, R. & Boccaccini, A. R. Tissue engineering of electrically responsive tissues using polyaniline based polymers: a review. *Biomaterials* **35**, 9068–9086 (2014).
87. Kai, D., Prabhakaran, M. P., Jin, G. & Ramakrishna, S. Polypyrrole-contained electrospun conductive nanofibrous membranes for cardiac tissue engineering. *J. Biomed. Mater. Res. A* **99**, 376–385 (2011).
88. Navaei, A. et al. Gold nanorod-incorporated gelatin-based conductive hydrogels for engineering cardiac tissue constructs. *Acta Biomater.* **41**, 133–146 (2016).
89. Pok, S. et al. Biocompatible carbon nanotube-chitosan scaffold matching the electrical conductivity of the heart. *ACS Nano* **8**, 9822–9832 (2014).
90. Mihic, A. et al. A conductive polymer hydrogel supports cell electrical signaling and improves cardiac function after implantation into myocardial infarct. *Circulation* **132**, 772–784 (2015).
91. Wang, W. et al. An injectable conductive hydrogel encapsulating plasmid DNA-eNOs and ADSCs for treating MI. *Biomaterials* **160**, 69–81 (2018).
92. Liang, S. et al. Paintable and rapidly bondable conductive hydrogels as therapeutic cardiac patches. *Adv. Mater.* **30**, 1704235 (2018).
93. He, S. et al. The conductive function of biopolymer corrects myocardial scar conduction blockage and resynchronizes contraction to prevent heart failure. *Biomaterials* **258**, 120285 (2020).
94. Motealleh, A. & Kehr, N. S. Nanocomposite hydrogels and their applications in tissue engineering. *Adv. Healthc. Mater.* **6**, 1600938 (2017).
95. Lei, Z. Y. & Wu, P. Y. A highly transparent and ultra-stretchable conductor with stable conductivity during large deformation. *Nat. Commun.* **10**, 3429 (2019).
96. Noshadi, I. et al. Engineering biodegradable and biocompatible bio-ionic liquid conjugated hydrogels with tunable conductivity and mechanical properties. *Sci. Rep.* **7**, 4345 (2017).
97. Liu, Y. et al. One zwitterionic injectable hydrogel with ion conductivity enables efficient restoration of cardiac function after MI. *Chem. Eng. J.* **418**, 129352 (2021).
98. Zhao, Q. & Li, Z. J. Angiogenesis. *BioMed. Res. Int.* **2015**, 135861 (2015).
99. Awada, H. K., Johnson, N. R. & Wang, Y. D. Sequential delivery of angiogenic growth factors improves revascularization and heart function after MI. *J. Control. Release* **207**, 7–17 (2015).
100. Yuan, Z. Z. et al. Injectable citrate-based hydrogel as an angiogenic biomaterial improves cardiac repair after MI. *ACS Appl. Mater. Interfaces* **11**, 38429–38439 (2019).
101. Massion, P. B., Feron, O., Dessy, C. & Balligand, J. L. Nitric oxide and cardiac function ten years after, and continuing. *Circ. Res.* **93**, 388–398 (2003).
102. Lundberg, J. O., Weitzberg, E. & Gladwin, M. T. The nitrate-nitrite-nitric oxide pathway in physiology and therapeutics. *Nat. Rev. Drug Discov.* **7**, 156–167 (2008).
103. Qin, Q. et al. Exogenous NO triggers preconditioning via a cGMP-and mitoKATP-dependent mechanism. *Am. J. Physiol.-Heart C.* **287**, H712–H718 (2004).
104. Yao, X. P. et al. Nitric oxide releasing hydrogel enhances the therapeutic efficacy of mesenchymal stem cells for MI. *Biomaterials* **60**, 130e140 (2015).
105. Chen, G. Q. et al. A Mixed Component supramolecular hydrogel to improve mice cardiac function and alleviate ventricular remodeling after acute MI. *Adv. Funct. Mater.* **27**, 1701798 (2017).
106. Vong, L. B. et al. Novel angiogenesis therapeutics by redox injectable hydrogel-Regulation of local nitric oxide generation for effective cardiovascular therapy. *Biomaterials* **167**, 143e152 (2018).
107. Rufaihah, A. J. et al. Enhanced infarct stabilization and neovascularization mediated by VEGF-loaded PEGylated fibrinogen hydrogel in a rodent myocardial infarction model. *Biomaterials* **34**, 8195–8202 (2013).
108. Munarin, F., Kant, R. J., Rupert, C. E., Khoo, A. & Coulombe, K. L. K. Engineered human myocardium with local release of angiogenic proteins improves vascularization and cardiac function in injured rat hearts. *Biomaterials* **251**, 120033 (2020).
109. Lee, S. et al. Human-recombinant-elastin-based bioinks for 3D bioprinting of vascularized soft tissues. *Adv. Mater.* **32**, 2003915 (2020).
110. Noor, N. et al. 3D printing of personalized thick and perfusable cardiac patches and hearts. *Adv. Sci.* **6**, 1900344 (2019).
111. Motterlini, R. & Otterbein, L. E. The therapeutic potential of carbon monoxide. *Nat. Rev. Drug Discov.* **9**, 728–U24 (2010).
112. Wang, W. L., Ge, T. Y., Chen, X., Mao, Y. C. & Zhu, Y. Z. Advances in the protective mechanism of NO, H_2S, and H_2 in myocardial ischemic injury. *Front. Cardiovasc. Med.* **7**, 588206 (2020).
113. Kim, I. et al. Supramolecular carbon monoxide-releasing peptide hydrogel patch. *Adv. Funct. Mater.* **28**, 1803051 (2018).
114. Liang, W. et al. Conductive hydrogen sulfide-releasing hydrogel encapsulating ADSCs for myocardial infarction treatment. *ACS Appl. Mater. Interfaces* **11**, 14619–14629 (2019).
115. Shiekh, P. A., Singh, A. & Kumar, A. Oxygen releasing antioxidant cryogel scaffolds with sustained oxygen delivery for tissue engineering applications. *ACS Appl. Mater. Interfaces* **10**, 18458–18469 (2018).