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REVIEW

Advanced Nanomedicine Approaches for Myocardial Infarction Treatment

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Abstract: Myocardial infarction, usually caused by the rupture of atherosclerotic plaque, leads to irreversible ischemic cardiomyocyte death within hours followed by impaired cardiac performance or even heart failure. Current interventional reperfusion strategies for myocardial infarction still face high mortality with the development of heart failure. Nanomaterial-based therapy has made great progress in reducing infarct size and promoting cardiac repair after MI, although most studies are preclinical trials. This review focuses primarily on recent progress (2016–now) in the development of various nanomedicines in the treatment of myocardial infarction. We summarize these applications with the strategy of mechanism including anti-cardiomyocyte death strategy, activation of neovascularization, antioxidants strategy, immunomodulation, anti-cardiac remodeling, and cardiac repair.

Keywords: myocardial infarction, nanomaterials, nanomedicine delivery system

Introduction

Myocardial infarction (MI), as a most severe type of ischemic heart disease, is emerging as the single largest cause of death worldwide, leading to a huge challenge to healthcare globally. MI is usually induced by atherosclerosis, as atherosclerotic plaques accumulate within the coronary arterial walls that severely limit or even block the flow of blood to the heart, leading to irreversible ischemic myocardial damage within hours. The only way to rescue myocardium from myocardial ischemia is timely reperfusion. Primary percutaneous coronary intervention, coronary artery bypass grafting, or thrombolysis are current gold-standard therapies to open the occluded artery. However, timely revascularization could not only rescue the viability of the cardiomyocytes but also cause ischemia-reperfusion injury due to a burst of oxidative stress and could further aggravate cardiomyocyte death in the short term.[1,2] Due to the negligible regeneration ability of cardiomyocytes, the salvage of myocardium from damage during the ischemic and reperfusion periods is a critical step for MI treatment.

Over subsequent days after MI, injured cardiomyocytes or cell debris trigger an inflammatory reaction with the release of pro-inflammatory cytokines that facilitate the infiltration of immunocytes such as macrophages to clear the damaged cardiomyocytes. Macrophages could also release pro-inflammatory cytokines and pro-angiogenic factors to promote angiogenesis and cardiac regeneration. However, the inflammatory response also leads to further infarct expansion until the transition of macrophages from inflammation to repair.[3] The repair stage is characterized by the activation of fibroblasts to myofibroblasts, accompanied by collagen matrix deposition and scar formation. Since myofibroblasts cannot provide the systolic and diastolic function of cardiomyocytes, chronic remodeling occurs over several weeks. Compensatory mechanisms including ventricular dilatation occur but fail, leading to damaged ventricular function and eventually heart failure.[3,4]

Current cardioprotective drugs are largely derived from these identified key processes after MI, such as antiplatelet drugs, angiotensin II-receptor blockers, and angiotensin-converting enzyme inhibitors, although the therapeutic outcomes are unsatisfactory. Novel and effective avenues are required to solve the fundamental issue of cardiomyocyte death as well as to address key progresses in the progression of heart failure. It is challenging to achieve effective drug delivery in

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a beating heart compared with other diseases such as tumors. For one reason, myocardial uptake is relatively low due to the special structure of the heart and non-targeted drug distribution, which may lead to adverse off-target effects. In addition, current drugs such as small molecules, proteins or peptides, growth factors, and cytokines usually have low solubility and stability, which makes them unable for relatively high-dose and long-term drug delivery that is needed for post-MI treatment.[5]

Recent advances in nanomedicines that use nanomaterials as carriers to deliver cargo for either therapeutic or imaging purposes showed superior advantages for the treatment of a variety of diseases.[6,7] Nanomaterials, which are designed and fabricated in nanoscale, exhibit unique properties compared to traditional free drugs. Particularly, nanomaterials with a size larger than 8nm showed relatively long circulation time due to their ability to avoid kidney clearance and capture from the reticuloendothelial system after surface modification. Meanwhile, nanomaterials can enter and accumulate more easily in the lesion site in both passive and active ways. Besides, nanomaterials could be tuned with controllable physical or chemical properties to optimize their drug pharmacokinetics, allowing for active targeting or other specific functions in vivo.[8] Given the mentioned advantages of nanomaterials compared with traditional free drugs, nanomaterials are expected to contribute to huge progress in MI diagnosis and therapy. Indeed, numerous nanomaterials have been designed as nanocarriers for therapeutic delivery for MI treatment in the past several years. However, the progress of nanomedicines in MI is still in its infancy for few nanomedicines have entered preclinical and clinical trials. We summarize the current progress in nanomedicine-mediated MI treatment, classified by treatment mechanisms such as cardiomyocyte death, angiogenesis, inflammation, and cardiac repair in the progression of MI, as well as outline the future promising directions (Figure 1).

Nanomaterials and Delivery Systems for Preclinical Studies

Multiple nanomaterials have been explored for MI treatment as nanocarriers such as polymeric nanoparticles, lipid nanoparticles, inorganic nanoparticles, and biomimetic nanomaterials. Since their characteristics have already been extensively discussed in other reviews, a summary of their applications for MI treatment was made here in this review. Polymeric NPs, which consist of blocks of different hydrophobicities, have attracted considerable attention for MI treatment due to their good biocompatible and biodegradable property. Furthermore, polymeric NPs own extensive

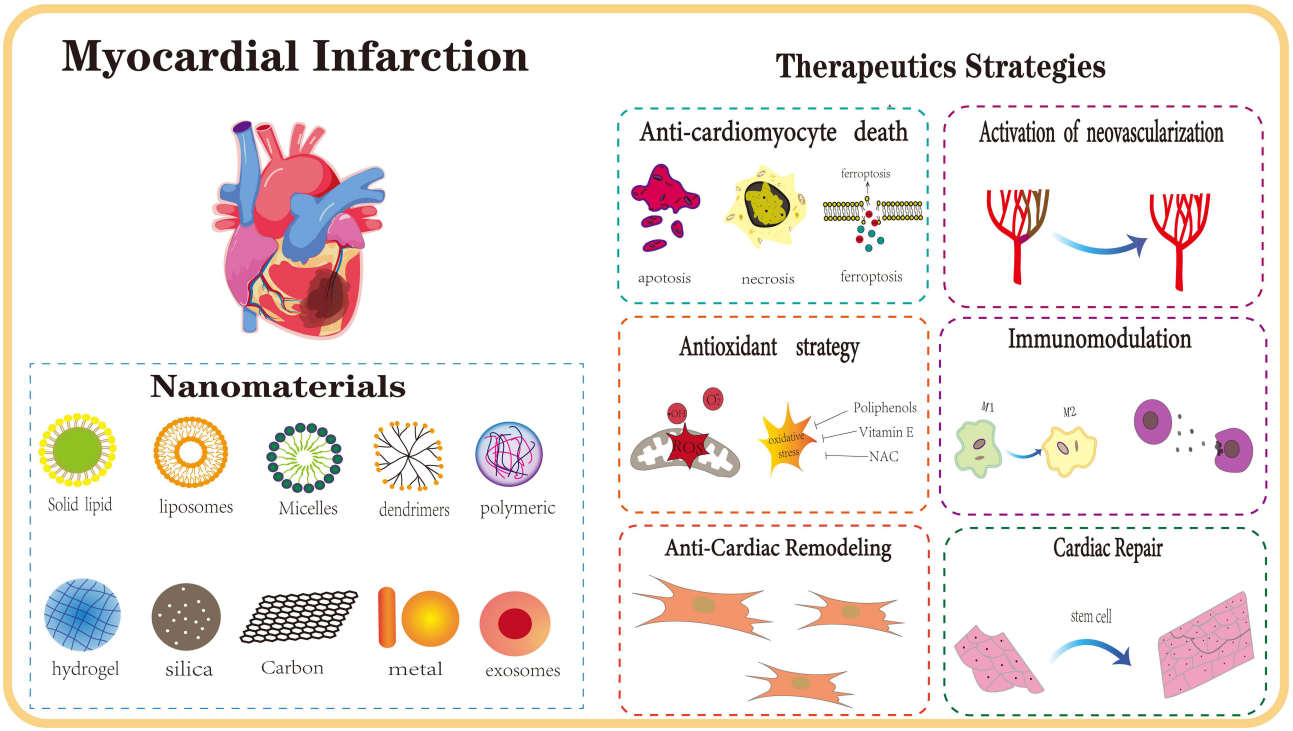

Figure 1 Schematic illustration of therapeutic strategies of nanomaterials of myocardial infarction.

modifiable end groups that enable easy modification for encapsulating therapeutics.[9,10] To date, the most studied polymer NPs for MI treatment include hyaluronic acid (HA), poly(lactic-co-glycolic acid) (PLGA)-based NPs, hydrogels, and network-like scaffolds. For example, hydrogels as insoluble three-dimensional (3D) polymeric networks could not only carry biologically active components in situ but also provide structural support and function as reparative materials for cardiac repair.[11] Liposomes are also well explored to deliver therapeutics for MI treatment. Liposomes are self-assembled vesicles consisting of a hollow core surrounded by a lipid bilayer shell. Various hydrophilic and hydrophobic therapeutics could be loaded inside the liposomes due to their unique amphiphilic properties.[12] Inorganic nanoparticles such as gold, iron, and silica nanoparticles are also widely used as delivery systems to achieve effective drug delivery to the myocardium. Except for being pure nanocarriers, they show extra characteristics due to their unique electrical or magnetic properties. For example, Fe_3O_4 nanoparticles could target specifically to the infarcted site under the guidance of magnetic fields, while AuNPs could promote fast transfer of electrical signals among cardiomyocytes, promoting functional assembly of the cardiac implants.[13–15] Biomimetic nanomaterials are also widely developed for MI therapy by using various cell membranes and extracellular vesicles (EVs) to delay the clearance of MPS and help NPs accumulate in the infarcted cardiac site.[16] Among the above-discussed delivery systems, the traditionally well-studied polymeric NPs and liposomes are the most widely used with new compositions explored to enhance their delivery ability. In addition, more and more studies are using new types of EVs and biomimetic membranes derived from various cells to improve drug delivery efficiency. Still, a uniform standard is necessary to evaluate drug delivery efficiency among those different nanoparticles, especially for further clinical translation.

Ways for therapeutic drug delivery to the infarct site mainly include intramyocardial injection, intracoronary injection, epicardial cardiac patch placement, intrapericardial injection, and intravenous injection. Intramyocardial injection could directly reach the site of myocardial infarction, but the running off of drugs and the low retention could compromise the efficacy. Meanwhile, the operation requires high conditions due to the invasive procedures as the unstable nature of the ventricle wall brings a high risk of the intramyocardial injection itself.[17] For intracoronary injection, a large quantity of drugs could be irrigated to the infarct site. It is simple, easy to use, and is the preferred way for therapeutic stem cell delivery.[18] A heart patch is a scaffold layered on the heart to provide physical support for the damaged heart as well as deliver therapeutic drugs to the pericardium for targeted delivery. It is an attractive option to deliver therapeutic cells or bioactive factors for cardiac repair. Compared to heart patches, intrapericardial injection of hydrogel is considered a relatively low-invasive method to deliver hydrogel for in situ cardiac patch formation. Hydrogels that contain therapeutic stem cells or various drugs could form a patch-like structure in the pericardial cavity after injection.[19] Intravenous injection is a feasible way for non-invasive drug delivery. It has low risk and low cost, but relatively low drug delivery efficiency to the myocardium.[18]

Nanomedicine Mediated Therapeutics Strategies for MI

Anti-Cardiomyocyte Death Strategy

Rescue myocardial injury from ischemia is key for the prognosis of MI due to the poor regeneration ability of cardiomyocytes. Adjunct ways to protect cardiomyocytes from death are needed to reduce infarct size and improve the prognosis of patients. Several common modes of cell death such as necrosis, apoptosis, necroptosis, pyroptosis, and relatively newly found ferroptosis all contribute to cardiomyocyte death during myocardial infarction, although the proportion of each form of cell death that contributes to CM death is unclear.[20] Current progress for nanomedicines that target CM death mainly includes nanocarriers loaded with a series of microRNAs, some preclinical or clinical drugs, and exosomes that mainly target cardiomyocyte apoptosis and necrosis (Table 1).

Nucleic Acid Nanomedicines to Inhibit Apoptosis or Necrosis

MicroRNAs are small non-coding RNAs that play an important regulatory role in the progression of MI at a post-transcriptional level. Numerous studies have reported the role of microRNAs in inhibiting cell apoptosis during MI, making them a promising way in MI preclinical treatment trials.[38] As a kind of nucleic acid therapy, microRNAs have notable limitations such as poor stability, off-target effect, limited tissue targeting and absorption, and fast clearance, thus studies have emphasized applying various nanoparticles to deliver microRNAs systemically trying to overcome the above limitations.

Table 1 Anti-Cardiomyocyte Death Strategy

Formulations	Therapeutic Agents	Carrier	Ref
Nucleic acid nanomedicines to inhibit apoptosis or necrosis			
Hep@PGEA/miR-499	miR-499	PGEA	[21]
DGL-loaded AMO-1	Anti-miR-1 antisense oligonucleotide	DGL	[22]
DGL-loaded miR-1 inhibitor	miR-1 inhibitor	DGL	[2]
miR21-EVs	miR-21	EVs	[23]
cT-miR-21-LIPs	miR-21	Liposomes	[24]
CM-miR-21-MSN	miR-21	MSN	[25]
PAMAM-His-miR	miR-214-3p, miR-194-5p, or antagomiR-122-5p	PAMAM	[26]
RGD-PEG-PLA/miR-133	miR-133	PLA	[27]
nHA-CLPs-miR-153-3p	miR-153-3p	Liposomes	[28]
F-silica-miR-24	miR-24	Silica NP-based PEI	[29]
F-CNT-caspase 3 siRNA	Caspase 3 siRNA	Carbon nanotube	[30]
Nanomedicines that target mitochondria-related apoptosis or necrosis			
Mdivi 1-NPs	Mitochondrial division inhibitor 1	PLGA NPs	[31]
CsA@PLGA-PEG-SS31	Cyclosporin A	PLGA-PEG	[32]
PLGA-CsA	Cyclosporin A	PLGA	[33]
Other strategies that target cardiomyocyte death			
EMMPRIN-NAP9	Extracellular matrix metalloproteinase inducer	Magnetic NPs	[34]
Melanin-PVP	Melanin	PVP NPs	[35]
Quercetin-MSNs	Quercetin	MSNs	[36]
mPEG- icariin NPs	Icariin	PEG monomethyl ether	[37]
ANP/TPP-baicalin-LPNs	Baicalin	Liposomes	[37]

For instance, in 2018, novel heparin NPs were fabricated by Nie and coworkers to deliver miR-499 to the infarct site to inhibit cardiomyocyte apoptosis. Overexpression of MiR-499 has been reported to inhibit apoptosis or promote proliferation of cardiomyocytes. To fabricate heparin NPs with the ability of self-accelerating nucleic acid release, disulfide bridged heparin was used as the core and then modified with a low-toxicity poly(glycidyl methacrylate) (PGEA) cationic shell, which assembled miR-499 through electrostatic interaction. The disulfide bonds could be reduced by increased glutathione amounts in the lesion site during MI, which makes the particles redox responsive. The reduced disulfide bonds would breakdown the heparin core and accelerate the release of condensed miR-499 inside PGEA shells. The NPs (Hep@PGEA/miR-499) demonstrated efficient cellular uptake, efficient miR-499 delivery, and higher efficiency in inhibiting apoptosis in vitro. Also, the in vivo results showed that Hep@PGEA/miR-499 demonstrated improved targeting ability and reduced cardiomyocyte apoptosis in the infarcted heart, and smaller lesion areas.[21] In the same year, Xue and coworkers constructed dendrimer-based nano vectors to deliver MicroRNA-1 inhibitors to the infarct site for MI treatment. MiR-1 overexpression was found to promote cardiomyocyte apoptosis by inhibiting anti-apoptosis protein expression such as PKCε and Bcl-2; thus, the author group used an anti-miR-1 antisense oligonucleotide (AMO-1) as miR-1 inhibitor to decrease CM apoptosis in the progression of MI. The dendrimer poly-L-lysine (DGL) was decorated with angiotensin II type 1 ligand to help NPs target the early stage of the ischemic heart. The NPs (DGL-loaded AMO-1) were shown to successfully target the infarcted heart and significantly reduce CM apoptosis in the infarcted zone in vivo.[22] Later, in 2020, the same group improved the fabrication of DGL-loaded AMO-1 where the angiotensin II type 1 ligand was substituted with low molecular weight heparin (LMWH). LMWH is a commonly used anticoagulant that can enhance antithrombin activity and prevent microthrombus formation. The results showed that the new NPs (DGL-loaded miR-1 inhibitor with an LMWH shell) could overcome microvascular obstruction in microcirculation, improve the accumulation of NPs in the infarct area, decrease CM apoptosis, and improve MI treatment efficiency.[2]

MiR-21 has been reported to inhibit CM apoptosis and reduce myocardial infarct size by regulating downstream programmed cell death 4 (PDCD4) and PTEN genes. Several groups have delivered miR-21 with different carriers for MI treatment by either intramyocardial or intravenous injection. As an example, in 2019, Song and coworkers fabricated miRNA-21-enriched extracellular vesicles (miR21-EVs) to treat MI. MiR21-EVs were isolated from miRNA-21 over-expressed HEK293T cells. The results showed that miR21-EVs could efficiently deliver miRNA-21 into cardiomyocytes, reduce PDCD4 expression, and attenuate cell apoptosis in vitro. Meanwhile, intramyocardial injected miR21-EVs could drastically inhibit cell apoptosis and improve cardiac function.[23] Later, Li and coworkers used DSPE-PEG liposomes modified with anti-cardiac troponin T (cTnT) antibody to deliver miR-21 intravenously to injured myocardium. Anti-cTnT antibody was used for targeted delivery of miR-21 to the ischemic myocardium. The NPs were found to accumulate in the infarction area obviously and significantly improved cardiac function.[24] In another study, Yao and coworkers developed mesenchymal stem cell (MSC) membrane-coated mesoporous silica nanoparticles for miR-21 delivery for MI treatment. MSC membrane could help the particle to escape the recognition and clearance from the immune system and target the injured myocardium better. Specifically, the NPs were found to possess high miR-21 loading capacity and could be successfully uptaken by cardiomyocytes. Meanwhile, miR-21-NPs could significantly alleviate CM apoptosis induced by 24h hypoxia, preserve viable myocardium and augment cardiac functions in vivo.[25]

Aside from miRNAs mentioned above, various nanocarriers loaded with other miRNAs to could target cardiomyocyte apoptosis have also been reported for MI treatment. For example, Sayed and coworkers developed poly(amidoamine)-histidine (PAMAM-His) nanocarriers to deliver miR-214-3p, miR-194-5p, or antagomiR-122-5p to inhibit cardiomyocyte apoptosis in vitro. All these PAMAM-His nanoparticles could effectively prevent cardiomyocytes from Hypoxia/Reperfusion injury.[26] Later, in 2020, Sun and coworkers used polyethylene glycol (PEG)-polylactic acid (PLA) nanoparticles modified with an arginine-glycine-aspartic acid tripeptide (RGD) to deliver miR-133 to the infarct lesion. MiR133 was reported to regulate the SIRT3/AMPK pathway in myocardial tissue during MI. The existence of RGD could target activated platelets in the infarcted site helping NPs accumulate in the lesion site. The results demonstrated that RGD-PEG-PLA/miR-133 could significantly inhibit cardiomyocyte apoptosis and decrease cardiac damage.[27] Besides, hyaluronic acid (HA)-cationic liposomes (CLPs) complex loaded with miR-153-3p[28] and silica nanoparticle-based polyethyleneimine (PEI) delivery system loaded with miR-24[29] were also been explored to treat MI by inhibiting cardiomyocyte apoptosis. Similar to miRNAs, siRNA treatment as another nucleic acid therapy for specific gene silencing also shows potential for treating MI. For instance, Li and coworkers developed a functionalized single-walled carbon nanotube bound to caspase 3 siRNA trying to overcome these limitations of nucleic acid therapy. The results showed that intramyocardial injection of F-CNT-siRNA could successfully provide anti-apoptotic therapy by decreasing caspase 3 expression in the early stage of MI, as well as reducing the infarct size and improving ventricular remodeling.[30] In summary, nucleic acid nanomedicines were considered promising candidates for MI therapy by inhibiting myocardial apoptosis or necrosis. Despite this, the detailed mechanism of those nucleic acid nanomedicines to induce cardiomyocyte death is unclear, especially for some newly developed miR-NPs. In addition, most nucleic acid nanomedicines target apoptosis or necrosis, and few nanomedicines target relatively newly studied cell death modes such as ferroptosis, necroptosis, or pyroptosis, which may provide a breakthrough for MI therapy. In addition, how quantifying the suitable nucleic acid nanomedicines and evaluating their efficacy in the targeted injured myocardium is still difficult. Although nucleic acids are integrated with those nanostructures to enhance targetability, how to avoid overdose and the potential risk of uncontrollable mutagenesis in the heart or non-target organs is key for further clinical trials.

Nanomedicines That Target Mitochondria-Related Apoptosis or Necrosis

Mitochondria as a major organelle for ATP production, are important targets for cardioprotective strategy. The mitochondrial permeability transition pore (mPTP) is a non-specific channel located in the inner mitochondrial membrane. Dysfunctional mitochondria during MI lead to the sustained mPTP opening, which could mediate permeability changes of mitochondria and initiate both necrosis and apoptosis. In 2016, Ishikita and coworkers fabricated mitochondrial division inhibitor 1(Mdivi 1) loaded poly(lactic-co-glycolic acid) nanoparticles to inhibit mitochondria outer membrane permeabilization and protect myocardium from mitochondria-mediated cell death. The results demonstrated that Mdivi 1-NPs could successfully inhibit the translocation of Bax to mitochondria as well as inhibit the leakage of cytochrome

c from mitochondria to the cytosol in vitro. Meanwhile, intravenous injected Mdivi 1-NPs could effectively reduce infarcted size compared with control after myocardial IR injury.[31] Later, in 2019, Zhang et al used a typical nanocarrier PLGA-PEG to load Cyclosporin A (CsA) to inhibit cardiomyocyte apoptosis by targeting mitochondria. CsA is an immunosuppressive agent that could inhibit mitochondrial permeability transition pore (mPTP) opening by binding with cyclophilin D in the inner mitochondrial membrane. To improve NP accumulation in the mitochondria, a mitochondria-targeted peptide SS31 was used to guide the NPs to accumulate in the mitochondria of the myocardium. As shown in Figure 2a-c, CsA@PLGA-PEG-SS31 nanoparticles were spherical and uniformly distributed. It was also demonstrated that CsA could be successfully delivered into mitochondria by CsA@PLGA-PEG-SS31, which indicates the important role of SS31 moiety in this process (Figure 2d and e). Furthermore, the results demonstrated that CsA@PLGA-PEG-SS31 nanoparticle could successfully accumulate and penetrate in ischemic myocardium 1h post-intravenous injection in an MI/RI rat model (Figure 2f and g). Meanwhile, the NPs alleviated mitochondrial damage and effectively protected the myocardium from MI damage (Figure 2h).[32] Similarly, in 2021, Ikeda and coworkers fabricated poly-lactic/glycolic acid nanoparticles containing CsA and detected its effects in cyclophilin D deficiency mice. As expected, CsA nanoparticles could target mitochondrial injury and confer cardio-protection effects against MI injury.[33]

Other Strategies That Target Cardiomyocyte Death

An interesting study reported by Cuadrado and coworkers explored the possibility of extracellular matrix metalloproteinase inducer (EMMPRIN) for MI treatment. EMMPRIN is highly expressed in injured myocardium and could induce the activation of matrix metalloproteinase-2 (MMP-2) and MMP-9. The authors fabricated theranostic paramagnetic/fluorescent micellar nanoparticles assembled with the EMMPRIN binding peptide AP-9 (NAP9) to target EMMPRIN. Cardiac magnetic resonance scans showed an enhanced signal where NPs were injected; meanwhile, the injection of NPs significantly reduced myocardial cell death in vivo.[34] Later, in 2022, studies by the same group determined the effects of NAP9 in a pig model, and the data point toward NAP9 as a promising tool for MI treatment.[39] Besides, Liu and coworkers explored the potential of delivering melanin via polyvinylpyrrolidone (PVP) nanoparticles to treat sepsis-induced myocardial injury by inhibiting ferroptosis. The authors reported that intravenously injected Melanin-PVP improved cardiac function in vivo by suppressing iron-accumulation-induced ferroptosis. Meanwhile, a decrease in oxidative stress, inflammation, and cardiomyocyte death was demonstrated in vitro. This study introduced ferroptosis as a new therapeutic strategy for treating MI.[35]

Recently, nanoparticles loaded with effective traditional Chinese medicines were explored for MI therapy to target cardiomyocyte death. For instance, Liu et al developed quercetin-loaded mesoporous silica nanoparticles (Q-MSNs) for myocardial ischemia-reperfusion injury treatment. Q-MSNs could successfully inhibit cell apoptosis by activating the JAK2/STAT3 pathway, enhancing its protection on improving ventricular remodeling and cardiac function.[36] Zheng et al used PEG monomethyl ether (mPEG) as a nanocarrier for icariin (ICA) loading. mPEG-ICA NPs were found to decrease the apoptotic rate in the in vitro oxygen–glucose deprivation model.[40] Atrial natriuretic peptide and triphenylphosphonium dual ligands modified, baicalin-loaded nanoparticulate system was used by Wang et al for acute MI therapy, this baicalin-loaded dual ligand system showed a remarkable effect on infarct size reduction.[37]

Activation of Neovascularization

Although primary percutaneous coronary intervention enables timely rescuing of major coronary blood flow after MI, the occurrence of microvascular obstruction usually leads to poor wound healing, ventricular remodeling, and even heart failure. Thus, restoration of microvascular blood flow by regeneration of microcirculation is essential for heart regeneration after MI. Although the detailed mechanisms of coronary revascularization after MI are not well defined, the local proliferation of endothelial cells and endothelial progenitor cells and the migration of remote stem cells are all considered to contribute to this process. In addition, neovascularization is also supported by several growth factors and peptides, including retinoic acid, fibroblast growth factors, VEGFA, CXCL12, and thymosin β4 (Tβ4).[41,42]

In some studies, researchers mainly focused on using nanomaterials to deliver a range of growth factors, for promoting angiogenesis for MI treatment. Among those factors, vascular endothelial growth factors (VEGFs) are commonly used. For example, Oduk and coworkers fabricated VEGF-loaded PLGA nanoparticles to increase angiogenic

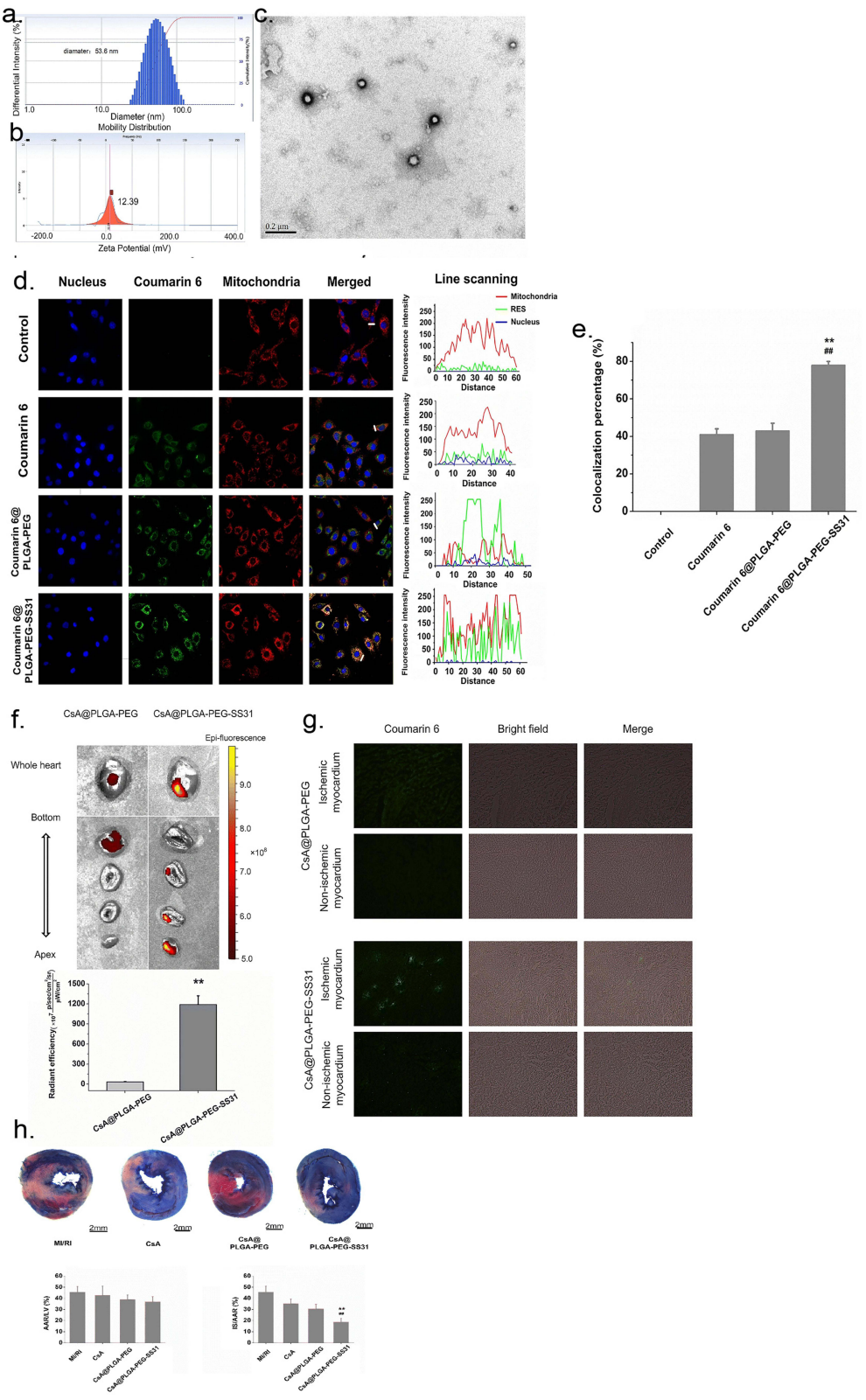

Figure 2 (**a**–**c**) In vitro characterization of CsA@PLGA-PEG-SS31including (a) size distribution, (**b**) zeta potential, and (**c**) TEM image. (**d** and **e**) Fluorescence images (**d**) and quantitative analysis (**e**) of intracellular trafficking of CsA@PLGA-PEG-SS31 in Hypoxia/Reperfusion treated H9c2 cells. **p < 0.01 versus coumarin 6 group, ##p < 0.01 versus coumarin 6@PLGA-PEG group. (**f**) Ex vivo fluorescence images and quantitative analysis of nanoparticles in MI/RI rat heart 1 h post-injection. **p < 0.01 versus CsA@ PLGA-PEG group. (**g**) Fluorescence microscope image of myocardium tissue 2 h post-injection. (**h**) Evans Blue and TTC staining of the myocardium, as well as the quantitative analysis of infarct size. **p < 0.01 versus CsA group; ##p < 0.01 versus CsA@PLGA-PEG group.

Notes: Reproduced with permission from Zhang CX, Cheng Y, Liu DZ et al. Mitochondria-targeted cyclosporin A delivery system to treat myocardial ischemia reperfusion injury of rats. *J Nanobiotechnology*. 2019;17(1):18.[32] Copyright 2019, BioMed Central. Creative Commons.

for MI treatment. Intramyocardial injection of VEGF-NPs into the peri-infarct region showed a continuous VEGF release for 31 days and increased vascular density significantly in the intramyocardial injection.[43] Likewise, in 2019 O'Dwyer and coworkers developed VEGF-loaded hydrogel for sustained release to enhance angiogenesis after MI. VEGF was encapsulated with polyglutamic acid (PGA) polypeptides and then incorporated into a hyaluronic acid hydrogel. The VEGF–PGA loaded hydrogel was demonstrated to be biocompatible and could provide sustained release of bioactive VEGF to the ischemic myocardium.[44] Similarly, Rocker and coworkers developed an injectable polymeric delivery system containing both VEGF and platelet-derived growth factor (PDGF) to promote blood vessel formation.[45] Meanwhile, another study reported by Qiao and coworkers demonstrated that a combination of heparin polysaccharide nanoparticles (HepNP) loaded with VEGF-A and VEGF-C could enhance both angiogenesis and lymphangiogenesis. Intravenously injected Hep@VEGF functional complexes at the dose ratio of 3:1 (Hep@VEGF-C vs Hep@VEGF-A) could substantially reduce scar formation and improve cardiac function.[46] Besides direct delivery of VEGF, VEGF-related gene therapy has also been explored. Nie and coworkers developed VEGF plasmids loaded nanocomplexes (Hep@PGEA) which enable self-accelerating nucleic acid release for MI treatment. The delivery of VEGF plasmids successfully facilitated angiogenesis in the infarct region.[21] Due to the unstable in vivo performance of VEGF as a protein, new techniques have been tried for the possibility of replacing VEGF with bioactive peptide sequences. Li and coworkers fabricated gadolinium-doped carbon dots (GCD-PEG) conjugated with VEGF mimetic peptide (VK) as theranostic nanomedicine for magnetic resonance imaging (MRI) and pro-angiogenesis therapy. The results showed that intravenously injected GCD-PEG-QK nanoparticles allow accurate detection of the infarcted site, as well as promote blood vessel formation and improve cardiac function.[47]

There are also other growth factors combined with nanocarriers used for angiogenesis. For instance, Huang and coworkers developed PEG-PLA nanoparticles to carry Tβ4 to stimulate neovascularization for intrinsic myocardial repair. The authors showed that fibrin-targeting CNP- Tβ4 leads to significant cardiac structural and functional improvements at 4 weeks for MI mice.[48] Awada and coworkers fabricated heparin-based coacervate-gel loaded with three complementary factors including tissue inhibitor of metalloproteinases-3 (TIMP-3) to reduce ECM degradation, basic fibroblast growth factor (FGF-2) for angiogenesis, and stromal cell-derived factor 1-alpha (SDF-1α) to recruit progenitor cells to the infarct region. The Protein-loaded Coacervate-Gel treatment exhibited revascularization and reduced ECM degradation and cardiomyocyte preservation, demonstrating the potential for comprehensive healing.[49] More recently, Wu and coworkers fabricated alginate sulfate-nanoparticles loaded with hepatocyte growth factor and insulin-like growth factor-1 for angiogenesis and cardiac repair in a porcine model for MI treatment. The authors reported that intramyocardial-injection of the nanoparticles showed a significant increase in left ventricular ejection fraction as well as improved myocardial remodeling.[50] However, the translation of those nanomedicines containing growth factors also faces limitations of low bioavailability and off-target adverse effects such as enhanced vascular leakage and tissue edema. Thus, evaluating the appropriate concentrations and improving targeted delivery are vital to avoid systemic toxicity.

In addition to using various growth factors, studies also tried other strategies to promote angiogenesis for MI treatment. For example, Li and coworkers investigated the capability of hydrogel with miR-21-5p loaded MSNs to enhance angiogenesis and regulate the immune-environment as miR-21-5p are reported to be highly expressed in endothelial cells and promote angiogenesis. As expected, the authors found that the injectable hydrogel (Gel@MSN/miR-21-5p) enabled controlled miR-21-5p delivery, while further promoting local neovascularization in a porcine model of MI, showing the potential for MI treatment.[51] Meanwhile, Chen and coworkers developed self-healing elastin-mimic peptide hydrogel (EMH) for the local delivery of salvianolic acid B (SaB) to promote angiogenesis for MI treatment. SaB-PDA/EMH hydrogel showed excellent biocompatibility and great mechanical strength, while the release of salvianolic acid B allowed for the proliferation and migration of endothelial cells, indicating the ability of SaB-PDA /EMH hydrogel to promote angiogenesis and reduce cardiac remodeling for MI treatment.[52] Another interesting work reported by Zhang and coworkers developed artificial hybrid nanosized cells (Hynocell) integrated with stem cell secretome coated with copper-containing protein fused cell membrane to boost vascular regeneration for MI treatment. Those bioactive factors that are secreted from hypoxic stem cells could improve the reconstruction of vasculature networks, while the copper-containing protein could facilitate NO release, providing synergistic effects for vascular

regeneration. The artificial Hynocell demonstrated a sustained release of NO and secreted factors, leading to promoted vascularization and enhanced cardiac function, indicating the synergistic role of Hynocell for cardiac repair.[53]

Antioxidants Strategy

Timely reperfusion is the only way to rescue myocardium from ischemia; however, reperfusion could lead to a more damaged myocardium in the short term due to a burst of oxidative stress, accompanied by the release of various proinflammatory cytokines. The clearance of excessive ROS in the infarct site is critical for decreasing Ischemia/Reperfusion-related tissue damage. Several pathways could contribute to excessive ROS accumulation in the infarcted site. For instance, the NADPH oxidase family (NOXs) are the only enzymes that could catalyze the production of ROS. Among NOXs, NOX1, NOX2, and NOX4 are mainly localized in the myocardium. In addition, the mitochondrial electron transport chain (ETC) is also a source of oxidative damage, because the electron leakage from ETC triggers ROS generation. In addition, mitochondrial Ca^{2+} overload and the following opening of mitochondrial permeability transition pore (mPTP) are key contributors to ROS overproduction.[54]

Since mitochondria are a major source of intracellular ROS, the clearance of mitochondrial ROS in ischemic myocardium has been considered a key target for I/R. Cheng and coworkers developed a mitochondria-targeted antioxidant delivery system for the treatment of I/R injury. PLGA nanoparticles were used to carry a powerful ROS scavenger resveratrol (RSV) modified with ischemic myocardium-targeted peptide (IMTP) and mitochondria-targeted peptide SS-31. The author showed that the nanoparticle could successfully accumulate in the ischemic site, concentrate in the mitochondria, and exert an effective therapeutic efficacy for I/R.[55] Later, Zhang and coworkers explored mitochondria-targeted hybrid enzymes as superoxide scavengers for IR treatment. Nanozymes are a new type of artificial enzymes with lower cost and higher stability when compared with natural enzymes. The author fabricated this nano-enzyme by choosing ferritin-based protein as the protein scaffold and MnO_2 particles as the enzyme active center. The MnO_2 Fenozymes could target myocardial mitochondria successfully and showed SOD and catalase-like activities, demonstrating a protective advantage in vivo under mitochondrial oxidative injury in I/R mice.[56]

Several nanomaterials have been reported with intrinsic antioxidative activities. For instance, Zhang and coworkers successfully delivered tetrahedral DNA nanostructures to the infarct site to reduce oxidative damage. The author showed that tetrahedral DNA nanostructures could significantly decrease oxidative damage and apoptosis by reducing ROS production in vitro.[57] More recently, Sun and coworkers designed self-sustaining selenium-embedded nanoparticles (SSSe NPs) to eliminate ROS for MI treatment. SSSe NPs were demonstrated to effectively reduce cardiomyocyte apoptosis and ferroptosis through ROS elimination. In addition, Se released by SSSe NPs was found to promote the transformation of endogenous antioxidant GPx4 for persistent ROS clearance. SSSe NPs mediated antioxidant strategy successfully prevented LV remodeling and restored cardiac function, providing a promising way of tissue repair for MI.[58] Recently, gold nanoparticles[59] and cerium oxide nanoparticles[60,61] have attracted attention for their antioxidant and anti-inflammatory properties. For instance, Im and coworkers synthesized copper-deposited ceria nanoparticles (CuCe NPs) for synergistic antioxidant therapy for MI therapy. Besides the antioxidant effects of pristine ceria nanoparticles themselves, the copper release from nanoparticles could function as a cofactor for an antioxidant enzyme, superoxide dismutase 1 (SOD1), which could catalyze the clearance of superoxide anions. Remarkably, the NPs presented improved antioxidant activity and improved cardiac functions for MI treatment in vivo.[61]

In addition, various drug-loaded nanomedicines were fabricated as effective antioxidants to scavenge excessive ROS. Bae and coworkers designed H_2O_2-responsive antioxidant copolyoxalates containing vanillyl alcohol (VA) which could target the site with ROS overproduction. The polymer nanoparticles PVAX could effectively suppress ROS generation caused by I/R in vivo.[62] Likewise, Zhou and coworkers developed melanin nanoparticles (MNPs)/alginate (Alg) hydrogels for cardiac repair by scavenging excessive ROS. MNPs were obtained from cuttlefish ink, which have antioxidant properties, and alginate were extracted from ocean algae, which provide mechanical support for the hydrogels. The results showed that MNPs/Alg hydrogels could successfully eliminate ROS against oxidative stress injury, as well as decrease inflammation, showing the potential to utilize natural biomaterials for cardiac repair.[63] Another interesting study reported by Wang and coworkers fabricated L-Arginine-loaded gold nanocages to produce NO to ameliorate ischemia/reperfusion injury. NO is a multifunctional molecule for the regulation of cardiovascular

homeostasis. L-Arginine-loaded gold nanocages were found to block ROS generation and maintain mitochondrial function in vitro, as well as inhibit myocardial apoptosis and fibrosis, and improve cardiac function in vivo, suggesting an effective treatment for MI.[64] In addition, PEGylated lipid nanoparticles loaded with puerarin,[65] schisandrin B,[66] Baicalin,[67] PLGA and PVA nanoparticles loaded with wogonin,[68] and PC nanoparticles loaded vanillic acid,[69] and hydrogel incorporated with puerarin[70] were all explored for MI therapy. All these nanoparticles demonstrated effective anti-oxidant ability and efficacy for MI treatment in vitro or in vivo. Other antioxidants such as bilirubin,[71] epigallocatechin gallate (EGCG), and coenzyme Q10 (CoQ10)[72] were also loaded inside polymer and liposome nanoparticles, respectively, to effectively eradicate ROS, mitigate myocardial cell apoptosis, and improve cardiac function.

Immunomodulation

Excessive cardiomyocyte death following myocardial infarction leads to acute inflammation at the initial stage. Injured cardiomyocytes and resident macrophages release pro-inflammatory cytokines such as IL-1, IL-6, and TNF-a, which could further recruit large quantities of neutrophils, monocytes/macrophages, and lymphocytes from circulation. These inflammatory cells provide the initial pro-regenerative function, for example, macrophages could undergo phagocytosis to clear necrotic cell debris as well as pro-angiogenesis by secreting various cytokines.[73] As the most abundant type of resident leukocytes, macrophages could be divided into pro-inflammatory M1 macrophages and pro-healing M2 macrophages. Lipopolysaccharide (LPS) or IFN-γcould induce the bone marrow-derived macrophage (BMDM) to differentiate pro-inflammatory M1 macrophages, while the addition of IL-4 and IL-13 could induce BMDM to be pro-healing M2 macrophages in vitro experiments. Also, macrophages could be divided into $CCR2^{+}$ MHC II ^{high}, $CCR2^{-}$ MHC II ^{high}, and $CCR2^{-}$MHC II ^{low} cells according to a more detailed classification. In brief, the minor group $CCR2^{+}$ macrophages could respond quickly to stimulations and release pro-inflammatory cytokines, while the major group $CCR2^{-}$ macrophages have low pro-inflammatory potentials. The transition from inflammation to repair in the MI site is strictly spatiotemporal controlled, followed by the resolution of inflammation, the activation of fibroblasts to myofibroblasts, and scar formation. The early excessive accumulation of pro-inflammatory immune cells and decreased transformation to reparative immune cells drive further infarct expansion at the MI site and aggravate cardiac dysfunction.[1,7] Thus, rebuilding the cardiac immune microenvironment is essential in inhibiting myocardial injury and promoting cardiac.

Nanomedicines That Alleviate the Accumulation of Pro-Inflammatory Immune Cells

Various nanomedicines have been developed to alleviate the accumulation of pro-inflammatory immune cells in the infarcted site at the early phase of MI (Table 2). In 2016, Nakano and coworkers reported using PLGA nanoparticles incorporating irbesartan to reduce inflammation after MI by inhibiting the recruitment of inflammatory monocytes to the IR heart. Irbesartan is an angiotensin II type 1 receptor blocker and has an agonistic effect of a peroxisome proliferator-activated receptor γ (PPARγ). The author showed that irbesartan-NP demonstrated a significant effect in reducing the infarct size 21 days after IR via PPARγ-dependent anti-inflammatory mechanisms.[74] Monocytes are recruited to the MI site via chemokine receptor CCR2. In 2018, Wang and colleagues fabricated PEG-DSPE micelles loaded with CCR2 antagonists to inhibit the infiltration of monocytes in the injured heart site. The micelles could successfully decrease the migration of $Ly6C^{high}$ inflammatory monocytes to the heart after MI by nearly 7% as well as significantly reduce the infarct size.[75] Similarly, in 2021, Ikeda and coworkers fabricated poly-lactic/glycolic acid nanoparticles containing pitavastatin to inhibit the recruitment of $Ly6C^{high}$-activated monocytes to the MI site through the inhibition of CCR2 mediated pathway, thus decreasing inflammation after MI.[33]

Injured cardiomyocytes could release damage-associated molecular patterns (DAMPs) at the early stage of inflammation, which could be recognized by innate immune systems through Toll-like receptor 4(TLR4), followed by the recruitment of neutrophils and monocytes/macrophages to the heart. To alleviate acute inflammation, Fujiwara et al delivered TAK-242, a chemical inhibitor of TLR4, with PLGA nanoparticles intravenously. The author showed that TAK-242-loaded PLGA-NPs could successfully accumulate in the heart and spleen in mice after MI injury. Moreover, the NPs decreased the accumulation of neutrophils and inflammatory monocytes in the heart after MI injury as well as inhibited the activation of monocytes/macrophages.[76] In addition, the pro-inflammatory cytokine tumor necrosis factor-a (TNF-a) is thought to be a critical factor in initiating pro-inflammatory cytokine cascades and functions as a double-edged sword in the early repair

Table 2 Immunomodulation Strategies

Formulations	Therapeutic Agents	Carrier	Ref
Nanomedicines that alleviate the accumulation of pro-inflammatory immune cells			
Irbesartan-NPs	Irbesartan	PLGA NPs	[74]
PEG-DSPE micelles - CCR2 antagonists	CCR2 antagonists	PEG-DSPE micelles	[75]
Pitavastatin-PLGA NPs	Pitavastatin	PLGA NPs	[33]
TAK-242-loaded PLGA-NPs	TAK-242	PLGA NPs	[76]
DNAzyme-AuNPs	DNAzyme	AuNPs	[77]
n-apo AI	Apolipoprotein apoA-I	Phosphatidylcholine	[78]
Neu-LPs	Neutrophil membranes	Liposomes	[79]
ABT263-PLGA	ABT263	PLGA NPs	[80]
Nanomedicines that skew macrophages towards the pro-healing M2 type			
Pioglitazone-NPs	Pioglitazone	PLGA NPs	[81]
PCL/DMI nanofiber patches	Itaconate-derivative dimethyl itaconate	PCL	[82]
L-Ag/R	MI antigens and rapamycin	Liposomes	[83]
DEXs	Dendritic cell-derived exosomes	Exosomes	[84]
Tregs biomimetic NPs	Cyclosporine A	Poly (5,5-dimethyl-4,6-dithio-propylene glycol azelate)	[85]
eNABs	Engineered neutrophil apoptotic bodies	MSNs	[86]
Mon-Exos	Monocyte membrane-decorated MSC-exosomes	Exosomes	[87]
Tβ4-MmEV	Thymosin β4	Macrophage-derived EVs	[88]
miRNA-21 NPs	miRNA-21	HA NPs	[89]
Nanomedicines for immunomodulation			
Hemin/HA-lipid particles	Hemin	Lipid NPs	[90]
Pitavastatin-loaded PLGA NPs	Pitavastatin	PLGA NPs	[91]
MTX-lipid core nanoparticles	Methotrexate	Lipid NPs	[92]
IL-5 loaded PLGA NPs	IL-5	PLGA NPs	[93]
Decellularized ECM hydrogel	Decellularized extracellular matrix	Lipid carriers-hydrogel	[94]
Rosmarinic acid hydrogel	Rosmarinic acid	DPA NPs-hydrogel	[95]
Upconversion cyanobacterium nanocapsules hydrogel	Upconversion cyanobacterium nanocapsules	Hydrogel	[96]
Berberine-loaded NPs	Berberine	Liposomes	[97,98]
Sal B and PNS NPs	Salvianolic acid B and panax notoginsenoside	Lipid-polymer hybrid NPs	[99]
Notoginsenoside R1 loaded MSN NPs	Notoginsenoside R1	MSNs	[100]
Sulforaphane NPs	Sulforaphane	Porous magnetic silica nanoparticles	[101]
Curcumin nanoparticles hydrogel	Curcumin	Ion-conductive hydrogel	[102]

process. In one study in 2016, Somasuntharam and coworkers synthesized DNAzyme gold nanoparticles for TNF-α knockdown to suppress TNF-α content during the acute inflammatory stage of MI. Experimental data showed that intramyocardial injection of 100μL DNAzyme functionalized gold nanoparticles at 100nM could significantly decrease TNF-α gene expression by nearly 30% and result in a strong anti-inflammatory effect and therapeutic benefits.[77] The main apolipoprotein apoA-I of high-density lipoprotein has been identified as a potential anti-inflammatory therapy for MI. Richart and coworkers fabricated Apo AI nanoparticles using plasma and soybean phosphatidylcholine (n-apo AI) for cardiac tissue recovery after MI. The author demonstrated that n-apo AI could successfully reduce the cardiac expression of chemokines, as well as decrease the cardiac number of neutrophils and monocytes, showing the ability of n-apo AI to reduce inflammatory response for MI treatment.[78] In a more recent study, Chen and coworkers explored the possibility of neutrophil-mimetic liposomes (Neu-LPs) by fusing neutrophil membranes with liposomes for adsorbing proinflammatory

cytokines during MI. The authors showed the ability of Neu-LPs to target the infarcted site, neutralize proinflammatory cytokines, as well as suppress intense inflammation, demonstrating the therapeutic efficacy for cardiac protection after MI.[79] Another interesting study conducted by Lee and coworkers reported the local delivery of a senolytic drug to ameliorate inflammatory responses and attenuate adverse remodeling for MI treatment. A senolytic drug ABT263 was loaded into PLGA nanoparticles to fabricate ABT263-PLGA, and the author demonstrated that the ABT263-PLGA could significantly ameliorate inflammatory responses by reducing the expression of pro-inflammatory molecules, promoting reparative macrophages via efferocytosis, showing the potential to restore impaired cardiac function.[80]

Nanomedicines That Skew Macrophages Towards the Pro-Healing M2 Type

Various nanomedicines have also been developed to skew macrophages towards the M2 type (Table 2). Peroxisome proliferator-activated receptor-gamma (PPARγ), which is a member of the nuclear receptor family, could inhibit the expression of NF-κB of macrophages and skew macrophages towards the pro-healing M2 type. Tokutome et al used a clinically approved potent PPARγ agonist, Pioglitazone carried by PLGA NPs to target monocytes/macrophages in the infarct site of a mouse IR model. Pioglitazone-NPs showed effective anti-inflammation effects and reduced infarct size in the mouse IR model.[81] Similarly, Nakkala and coworkers fabricated poly-ε-caprolactone (PCL) nanofibers loaded with itaconate-derivative dimethyl itaconate (DMI) to regulate inflammation after MI. Itaconate could be produced from aconitate, which is an intermediate product of the tricarboxylic acid (TCA) cycle. Itaconate has been recently reported to exert a promising immunomodulatory effect on macrophages. The authors demonstrated the effects of DMI to suppress the IL-23/IL-17 inflammatory axis as well as to promote the expression of antioxidant nuclear factor erythroid 2-related factor 2 target genes. It was observed that the PCL/DMI nanofiber patches could successfully regulate inflammation by maintaining inflammation at the initial stage and promoting anti-inflammatory activity at the tissue repair stage. Furthermore, PCL/DMI nanofiber patches exhibit reduced infarct area and improved ventricular function, thus showing excellent myocardial protection.[82]

In a more recent study, Kwon and coworkers synthesized liposomal nanoparticles loaded with MI antigens and rapamycin (L-Ag/R) trying to attenuate inflammation by regulating antigen-specific regulatory T cells (Tregs). Intradermal-injected L-Ag/R established an augmented, durable presentation of antigens by dendritic cells (DCs), followed by the effective induction of antigen-presenting dendritic cells and antigen-specific Tregs. L-Ag/R was found to attenuate inflammation in the myocardium by activating Tregs and polarizing M1 macrophages into M2 macrophages, with decreased adverse cardiac remodeling and enhanced cardiac function.[83] Besides, alginate hydrogel was employed by Zhang and coworkers to deliver dendritic cell-derived exosomes (DEXs) to improve cardiac function for MI treatment. The authors demonstrated that DEXs could activate Treg cells and shift macrophages to reparative M2 macrophages successfully both in vitro and in vivo. Meanwhile, the incorporation of DEXs with alginate hydrogel significantly enhanced the in vivo therapeutic effects of DEXs with enhanced cardiac function after MI.[84] More recently, Li and coworkers reported using cyclosporine A (CsA) loaded nanoparticles camouflaged with platelet membrane to mimic Tregs for immune-modulation after MI. The author demonstrated that Tregs mimics could significantly decrease inflammation and CM apoptosis, alleviate LV remodeling, and improve cardiac function markedly[85].

Inflammation resolution is a key step for injured myocardium towards tissue repair after MI. The resolution is initiated by neutrophil apoptosis and subsequent macrophage ingestion in the inflammatory zone. Macrophage ingestion, also called efferocytosis, could switch the macrophage phenotype followed by the secretion of anti-inflammatory factors. Bao and coworkers took advantage of this process and constructed engineered neutrophil apoptotic bodies (eNABs) using mesoporous silica nanoparticles loaded with hexyl 5-aminolevulinate hydrochloride (HAL) coated with natural neutrophil apoptotic body membrane. HAL was used to initiate the heme biosynthesis pathway to enhance anti-inflammatory effects. The results showed that eNABs could effectively reprogram macrophage function in the infarcted region and improve cardiac function after MI.[86] Stem cell-derived extracellular vesicles (EVs) have been reported to be effective in heart repair by promoting angiogenesis and modulating macrophage subpopulations after MI. By harnessing the ability of monocytes homing to the ischemic area, Zhang and coworkers fabricated monocyte membrane-decorated MSC-exosomes to promote specific targeting and heart repair after MI. The accumulation of monocyte membrane-decorated MSC-exosomes (Mon-Exos) exhibited a 1.65-fold increase in heart than non-targeted exosomes 2h post-intravenous

administration. Meanwhile, Mon-Exos significantly improved therapeutic outcomes in cardiac functions such as enhanced ejection fraction, fractional shortening, and less fibrosis remodeling. In addition, Mon-Exos exhibits the capacity to modulate macrophage subpopulation balance, with decreased MI cells and increased M2 polarity.[87] Cardiac-resident macrophages, as the ubiquitous components of the innate immune system, have been reported to play crucial roles in the maintenance of physiological homeostasis for tissue repair and remodeling. Here, Chen and coworkers developed monocyte membrane-modified thymosin β4 (Tβ4) loaded macrophage-derived extracellular vesicles (EVs) for cardiac repair for MI. As expected, the authors found that a large number of modified EVs could aggregate at the infarct site, showing the targeting ability of monocyte membrane to the injured myocardium after systemic administration. In addition, modified EVs significantly reduced myocardial fibrosis and increased angiogenesis, showing significant potential for MI therapy.[88] Nanoparticle-loaded microRNAs are also well studied for immunomodulation for MI treatment. For example, in 2018, Bejerano and coworkers fabricated hyaluronan-sulfate-loaded MiRNA-21 mimic nanoparticles (miRNA-21 NPs) to target cardiac macrophages at the infarct zone for the treatment of MI. The in vivo results showed that intravenously administrated miRNA-21 NPs could successfully accumulate in cardiac macrophages and promote reparative macrophages.[89]

Nanomedicines for Immunomodulation

Various nanomedicines have been reported to regulate the immune microenvironment for MI therapy (Table 2). Mordechai and coworkers encapsulated hemin into lipid-based particles to improve cardiac remodeling after MI. As an iron-containing porphyrin, hemin could activate heme oxygenase-1, which provides anti-inflammatory and cytoprotective effects. The results showed that intravenously injected hemin/HA-lipid particles at the dose of 10mg/kg in vivo could significantly improve infarct healing and repair by nearly 10%.[90] Moreover, Ichimura and coworkers reported the anti-inflammation effects of pitavastatin-loaded PLGA nanoparticles for MI treatment by activating the PI3K-Akt pathway in a rat IR model.[91] In 2017, Maranhão et al used an anti-inflammatory drug methotrexate (MTX) carried by lipid core nanoparticles to target inflammation after MI. MTX could promote the release of adenosine in various cells by disturbing folate metabolism, thus inhibiting the activation of various leukocytes. MTX-lipid core nanoparticles result in a remarkable reduction in infarct size and improvement in heart function for MI rats.[92]

Recently, Han and coworkers loaded interleukin-5 (IL-5) into PLGA nanoparticles camouflaged with neutrophilic membrane to alleviate inflammation and promote angiogenesis for MI treatment. IL-5 was proposed as a promising cardiac detoxification agent for cardiac repair after MI. Meanwhile, the neutrophilic membrane could help NPs infiltrate the infarcted region specifically. The authors found that the NPs demonstrated an enhanced eosinophil accumulation and decreased neutrophil-related cytokines in the injured heart, leading to decreased inflammation. Meanwhile, NPs also lead to increased angiogenesis and improved cardiac function, indicating the promise of a cardiac detoxification agent for MI therapy.[93] A cardiac extracellular matrix (ECM) hydrogel incorporated with nanostructured lipid carriers (NLCs) was employed by Wang and coworkers as a platform for cardiac repair. Decellularized extracellular matrix retains various structural proteins and growth factors that have been reported to benefit wound healing, improve cardiac repair, and affect fibroblast activation. The authors used NLCs to carry an anti-inflammation drug, colchicine, and then conjugated to decellularized extracellular matrix (ECM) hydrogel. ECM-NLC-colchicine hydrogel demonstrated sustained and localized release properties, meanwhile, leading to a significantly improved cardiac repair.[94] Similarly, Zhang and coworkers constructed an injectable conductive hydrogel with a smart release of rosmarinic acid to promote cardiac repair after MI. To realize the smart release, xanthan gum, and gelatin in hydrogel were crosslinked with pH/ROS -responsive imine bond and boronic ester bond. Meanwhile, polydopamine-rosmarinic acid nanoparticles were encapsulated into a hydrogel for anti-inflammation and anti-apoptosis effects. Also, conductive composites were added to enhance the conductivity and mechanical strength of the hydrogel. The multifunctional hydrogel could effectively restore cardiac function after MI, indicating the potential to promote cardiac repair for MI treatment.[95] Recently, another study reported by Liu and coworkers demonstrated that photoresponsive hydrogel-coated upconversion cyanobacteria nanocapsules (UCCy@Gel) could regulate the immune microenvironment for MI treatment. Cyanobacteria were first modified using upconversion nanoparticles (Figure 3a). The therapeutic efficacy of this hydrogel contributes to engineered cyanobacteria, which could consume oxygen to enhance the tolerance of CMs for hypoxia. The results showed that UCCy@Gel was able to release

photosynthetic oxygen under NIR irradiation (Figure 3b). Meanwhile, it was demonstrated that UCCy@Gel could significantly decrease pro-inflammatory cytokines (Figure 3c and d) and inhibit macrophage M1 polarization (Figure 3e-g), showing the potential for cardiac repair after MI.[96]

Various nanomedicines containing traditional Chinese medicines have also been explored for immune-modulation of MI, such as berberine, notoginsenoside R1, curcumin,[103] puerarin,[65,104] baicalin,[37] and tanshinone.[105,106] For instance, Allijn and coworkers explored the possibility of using liposome-encapsulated berberine to attenuate cardiac dysfunction after MI. It was found that berberine-loaded liposomes could inhibit IL-6 secretion in RAW 264.7 macrophages in vitro. Furthermore, the in vivo study showed that Berberine-loaded liposomes demonstrated a significantly enhanced cardiac function by 64% compared to control.[97] Similarly, Zhu and coworkers developed berberine-loaded PLGA nanoparticles coated with platelet membrane to decrease inflammation for MI treatment. The coated platelet membrane could help nanoparticles enriched in the infarcted myocardium. It is worth noting that the NPs displayed excellent therapeutic efficacy by significantly increasing the number of repaired macrophages and decreasing inflammatory macrophages and apoptotic cells in the infarcted site. Furthermore, the NP group exhibits an enhanced cardiac function, reduced collagen deposition, as well as improved angiogenesis effect, indicating a potential solution for MI treatment.[98] Notoginsenoside R1 was also used to target inflammatory cells to improve heart repair after MI.[99,100] For instance, Qiu and coworkers synthesized arginyl-glycyl-aspartic acid (RGD) conjugated lipid-polymer hybrid nanoparticles (RGD-S/P-LPNs) loaded with salvianolic acid B (Sal B) and panax notoginsenoside (PNS). Sal B, as traditional Chinese Medicine, has anti-inflammation effects by decreasing cytokine secretions such as tumor necrosis factor-α (TNF-α), and interleukin-1β (IL-1β). PNS, another traditional Chinese medicine, could modulate vascular tone. The hybrid nanoparticles RGD-S/P-LPNs were found to reduce the infarct size significantly compared with the control.[99] Later, in 2022, Li and coworkers fabricated notoginsenoside R1 loaded MSN nanoparticles to regulate inflammation after MI.[100] The anti-inflammatory sulforaphane (SFN), isolated from cruciferous vegetables, was loaded into porous magnetic silica nanoparticles (PMSNs) to target the infarcted site, mitigate levels of pro-inflammatory cytokines, and improve cardiac function for MI.[101] Recently, Shen and coworkers fabricated an ion-conductive hydrogel bioelectronic patch containing curcumin nanoparticles for real-time monitoring and heart repair. The ion-conductive hydrogel provided good elasticity, ultrahigh mechanoelectrical sensitivity, and reliable sensing capacity. Simultaneously, curcumin nanoparticles demonstrated the ability to regulate inflammatory microenvironment, reduce myocardial fibrosis, and effective MI repair.[102]

Among nanomedicine studies for MI therapy, considerable efforts have been made related to inflammation. As we mentioned above, inflammation is not considered as a barrier to cardiac repair after MI, the initial inflammation stage is critical for the following tissue repair. Thus, the accurate transition from inflammation to repair needs to be strictly regulated. However, a portion of the above-mentioned studies emphasize inflammation resolution, but not the following repair. Also, compared to the classic M1 and M2 macrophage classification, a more accurate classification strategy using CCR2 is recommended. In addition, the mechanism of some nanomedicines containing natural components to regulate inflammation is unclear, which limits their further application.

Anti-Cardiac Remodeling

Over subsequent days following acute myocardial infarction, a transition from inflammation to repair at the border zones occurs which is characterized by the activation of fibroblasts to myofibroblasts with collagen matrix deposition, leading to scar formation. Scar formation is critical to provide mechanical strength and prevent the ventricle from rupturing in the short term. However, due to the inability of myofibroblasts to provide the systolic and diastolic function like cardiomyocytes, chronic remodeling subsequently occurs with ventricular dilatation, activation of interstitial fibrosis, and decreased left ventricular (LV) function, which eventually contributes to heart failure.[1,7]

The study reported by Fan and coworkers explored MI-responsive hydrogels that could target upregulated matrix metalloproteinase-2/9 on the MI site and enable on-demand bFGF delivery for MI treatment. Briefly, bFGF was firstly fused with glutathione-S-transferase (GST) and MMP-2/9 cleavable peptide PLGLAG (TIMP) and then conjugated with collagen hydrogel modified with glutathione (GSH) to become GST-TIMP-bFGF/collagen-GSH hydrogels. The TIMP on the gels could respond to MMPs for on-demand bFGF release as well as inhibit the excessive degradation of the cardiac matrix. The authors demonstrated enhanced vascularization and ameliorated myocardium remodeling after intramyocardial

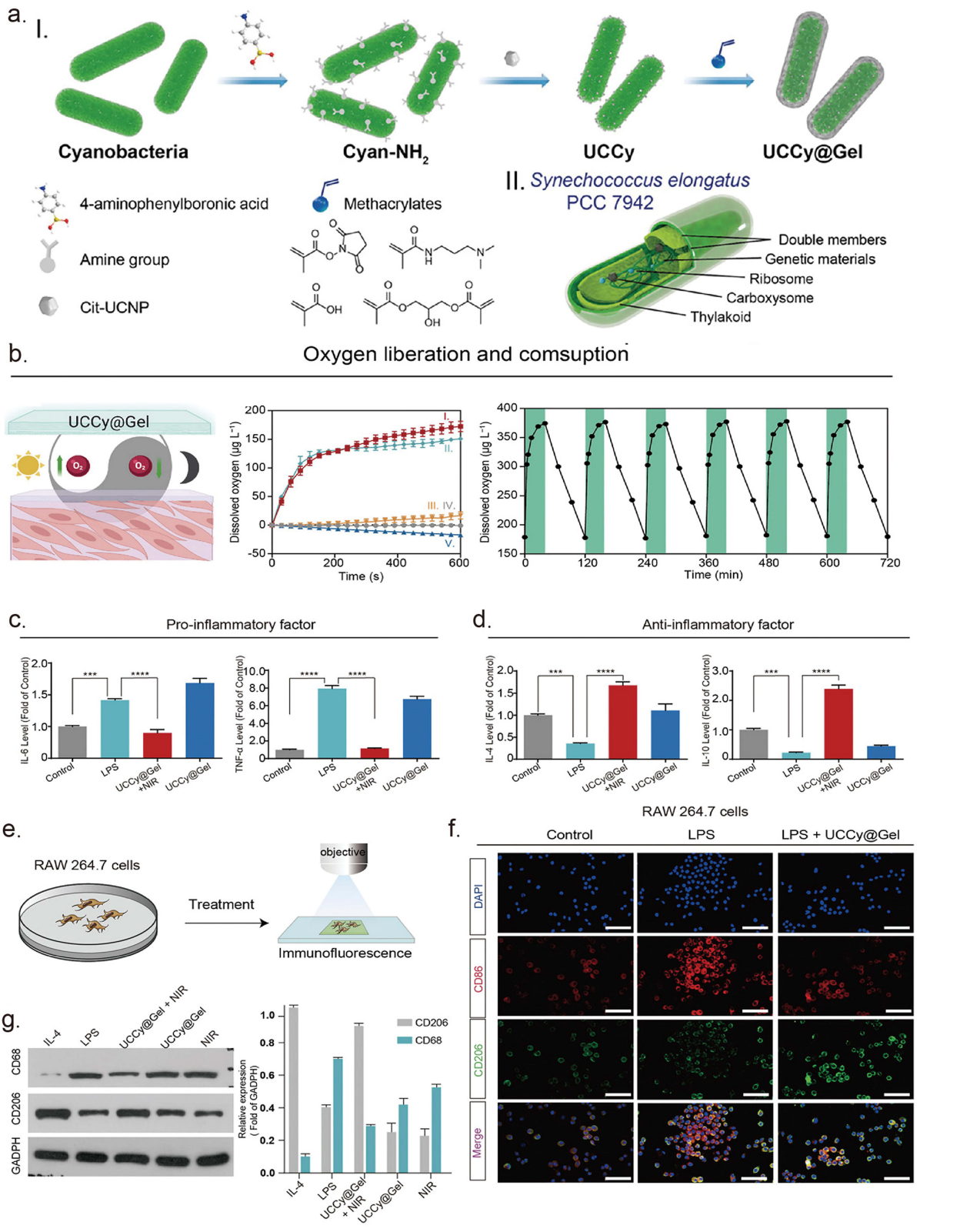

Figure 3 (**a**) Schematic diagram of UCCy@Gel preparation.(**b**) Time-oxygen liberation curves of UCCy@Gel under NIR light irradiation. (**c** and **d**) Expression levels of pro/anti-inflammatory factors of cells treated with/without UCCy@Gel. ***p < 0.001, ****p < 0.0001. (**e**–**g**) Fluorescence images and Western blot analysis of macrophage M1 and M2 phenotypic markers.

Notes: Reproduced with permission from Liu Y, Zhong D, He Y et al. Photoresponsive Hydrogel-Coated Upconversion Cyanobacteria Nanocapsules for Myocardial Infarction Prevention and Treatment. *Adv Sci (Weinh)*. 2022;9(30):e2202920.[96] Copyright 2022, Wiley-VCH GmbH. Creative Commons.

administration for MI.[107] Meanwhile, another study reported by Fan and coworkers developed a thermosensitive and fast gelation hydrogel system for bFGF release for MI treatment. The polymer NIPAAm, HEMA, and a macromer acrylate-oligolactide (AOLA) were used for hydrogel fabrication. The released bFGF could promote cardiac fibroblast survival, attenuate cardiac fibroblast differentiation into myofibroblasts, as well as promote angiogenesis. The bFGF-containing hydrogel demonstrated significant efficacy for MI treatment with enhanced cardiac function in vivo.[108] In a more recent study, Aziz and coworkers fabricated a polypyrrole-polycarbonate polyurethane elastomer to alleviate atrial fibrillation after myocardial fibrosis resulting from MI. This conductive and elastic bio-membrane could successfully promote synchronous contraction of isolated cardiomyocytes in vitro and further alleviate cardiac arrhythmias with epicardial implantation in vivo.[109] In addition, Ji and coworkers reported the development of a glutathione (GSH)-responsive nanoparticle platform carried with a sphingosine kinase 1 inhibitor, PF543, for heart-targeted drug delivery to treat fibrosis after MI. A sharp increase in cardiac GSH levels after MI was reported; meanwhile, PF543 was identified to decrease fibrosis through high-throughput drug screening. In particular, the authors encapsulated PF543 into Cysteine (Cys)-PDSA polymer, which is highly sensitive to GSH (Figure 4a and b). The study demonstrated that these NPs exhibited GSH-dependent drug delivery (Figure 4c), accumulated significantly in the heart after MI, and showed higher therapeutic efficacy for MI (Figure 4d and e).[110]

Besides chemical drugs, nucleic acid therapy has provided an alternative for anti-cardiac remodeling of MI therapy. For example, in 2016, reducible dendrimer polymers were employed by Lee and coworkers to transport relaxin-expressing plasmid DNA to the infarct site to ameliorate cardiac remodeling post-MI. Relaxin, as a pleiotropic hormone, has the capability of anti-inflammatory, vasodilatory, antiarrhythmic, and anti-fibrotic effects. The NPs were shown to significantly improve LV systolic function after MI in rats as well as showed favorable post-infarct cardiac ECM remodeling.[111] In a more recent study, Zhu and coworkers constructed lipid nanoparticles containing lncRNA– Tcf21 antisense RNA inducing demethylation (TARID) to target myocardial fibrosis. The authors first demonstrated the potential effects of Tcf21, which is derived from mesenchymal stem cell–derived extracellular vesicles (EVs) for cardiac remodeling. Later, the therapeutic effects of lncRNA–TARID-laden lipid nanoparticles to decrease cardiac fibrosis and promote cardiac repair were demonstrated in both mouse and porcine models of MI, indicating the potential use of this system for lncRNA therapy for cardiac fibrosis after MI.[112] Nanomedicines that target thrombus for spatiotemporal thrombolysis were also explored. For example, in 2018, Mihalko and coworkers designed fibrin-specific nanogels to reestablish blood flow and inhibit cardiac fibrosis simultaneously after MI. Core-shell (C/S) poly(N-isopropylacrylamide) nanogels were fabricated and encapsulated with a fibrinolytic protein (tissue plasminogen activator, tPA) and a small-molecule cell contractility inhibitor (Y-27632). tPA and Y-27632-loaded nanogels lead to rapid fibrin degradation and decreased cardiac fiber formation in vitro, as well as decreased infarct size and enhanced cardiac function after intracoronary injection in vivo.[113] A similar study was done by Guo and coworkers in 2022 who developed thrombus responsive phenylboronic acid (PBA) nanocarrier loaded with tPA and antioxidant molecular protocatechualdehyde (PC) to reopen the infarct artery for MI treatment.[114]

In the field of cardiac remodeling-related MI treatment, several studies have reported the possibility of direct genetic reprogramming therapeutics for converting fibroblasts to cardiomyocytes. For instance, in 2018, Ferreira and coworkers explored the potential of dextran-functionalized nanoparticles for fibroblast reprogramming into cardiomyocytes. Dextran-based functional nanoparticles loaded with two small molecules, CHIR99021 and SB431542, is developed for pH-triggered drug delivery. The in vitro results verified the effects of NPs in targeting cardiac fibroblasts for cellular reprogramming by stabilizing β-catenin (CHIR99021) and by preventing Smad3 nuclear translocation of (myo)fibroblasts (SB431542), respectively.[115] In addition, reprogramming of induced-cardiomyocytes (iCMs) from noncardiomyocytes is also a promising therapeutic way. Chang et al fabricated cationic gold nanoparticles (AuNPs) loaded with Gata4, Mef2c, and Tbx5 for cardiomyocyte reprogramming from fibroblasts. The results showed that the AuNP/GMT/PEI nano complexes could effectively recover cardiac function and scar area by efficiently converting fibroblasts into cardiomyocytes after MI.[116] Similarly, Muniyandi and coworkers synthesize PLGA-PEI nanocarriers loaded with miR-1 and miR-133a for genetic reprogramming of cardiac fibroblasts. The in vitro results showed a significant change in cardiac fibroblast phenotype to cardiomyocytes as verified with several markers.[117] Another interesting study published in the same year by Kim and coworkers developed nanogels that try to convert normal human dermal fibroblasts (NHDFs) into cardiomyocyte-like cells directly. The nanogels are fabricated based on

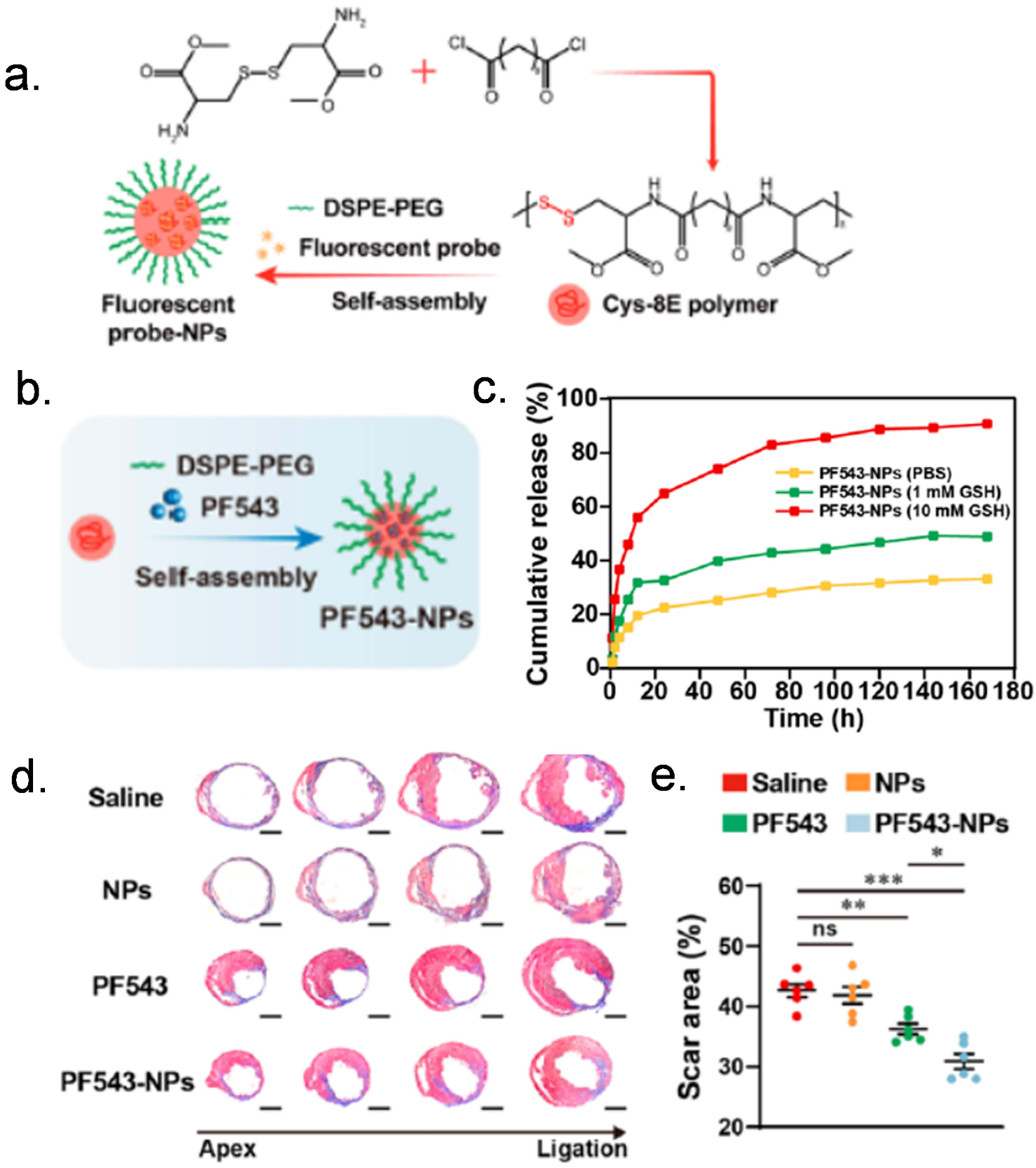

Figure 4 (**a**) Schematic illustration for the synthesis of Cys-8E NPs loaded with fluorescent probes-DiR. (**b**) Scheme of PF543 loading to Cys-8E NPs to form PF543-NPs. (**c**) Measurement of the in vitro drug release capacity of PF543-NPs in the presence of GSH at various concentrations. (**d** and **e**) Representative Masson-Trichrome staining (**d**) of heart cross sections 28 days post-MI with quantification (**e**) of scar size. ns, not significant, *p < 0.05, **p < 0.01, ***p < 0.001.
Notes: Reproduced with permission from Ji X, Meng Y, Wang Q et al. Cysteine-Based Redox-Responsive Nanoparticles for Fibroblast-Targeted Drug Delivery in the Treatment of Myocardial Infarction. *ACS Nano*. 2023;17(6):5421–5434. Copyright 2023, American Chemistry Society.[110]

carboxymethylcellulose (CMC) nanoparticles linked with three plasmids containing specific cardiomyocyte-related genes (GATA4, MEF2C, and TBX5) and 5-azacytidine (5-AZA) to promote stem cell differentiation. It was observed that transplanted cells could exhibit active pumping for 1 day.[118]

Nanomedicines containing traditional Chinese medicine that targets cardiac remodeling were also widely explored. For example, Mao and coworkers fabricated polymeric nanoparticles incorporating tanshinone IIA (tanshinone IIA-NPs) trying to attenuate post-infarction left ventricular (LV) remodeling. Tanshinone IIA could decrease collagen deposition in elastogenesis by activation of the PKA/CREB phosphorylation pathway in cardiac fibroblasts in vitro. The results showed that Tanshinone IIA significantly limited infarct expansion, improved cardiac function, and prevented left-ventricle dilation post-MI.[119] Later, in 2019, Wang and coworkers reported their ROS-sensitive hydrogel systems for Tanshinone IIA delivery for rebuilding post-infarcted cardiac functions. Polydopamine (PDA)-coated TIIA nanoparticles were first fabricated and then cross-linked within ROS-sensitive hydrogel. After intramyocardial injection, the hydrogel exhibited a high drug-loading ability with sustained drug release kinetics, leading to a significant improvement in cardiac functions.[120] In addition, in 2020, Martel and coworkers designed phenylboronic acid hyperbranched macromer-based hydrogel loaded with gold nanorods and Astragaloside IV nanodrugs for MI treatment. Astragaloside IV, isolated from Chinese medicine Radix astragali, has the effects of anti-apoptotic and anti-inflammation, while the addition of gold nanorods could enhance the conductivity of hydrogels. The hydrogel was found to effectively inhibit left ventricular remodeling and enhance cardiac function significantly after MI in rats.[121]

Cardiac Repair

Once damaged, the ability of the myocardium to regenerate is negligible. Current efforts towards cardiac repair mainly include cell-based therapies, control of cardiomyocyte proliferation, and cell reprogramming (Table 3).

Table 3 Cardiac Repair Strategies

Formulations	Therapeutic Agents	Carrier	Ref
Cell-based therapies			
ADSCs with neuregulin-PLGA MPs	Neuregulin	PLGA MPs	[122]
ADSCs with fullerenol/alginate hydrogel	n.a.	Fullerenol/alginate hydrogel	[123]
BASCs with Au@Pt/Alg hydrogel	n.a.	au@Pt/Alg and hydrogel	[14]
ADSCs with melatonin-loaded PLGA NPs	Melatonin	PLGA NPs	[124]
ADSCs with AuNPs chitosan-silk fibroin hydrogel	n.a.	AuNPs and chitosan-silk fibroin hydrogel	[125]
ADSCs with ECM/silk proteins NPs	n.a.	ECM/silk proteins NPs	[125]
ADSCs with inverse opals	n.a.	Inverse opals	[126]
ADSCs with simvastatin NPs	Simvastatin	Polymer NPs	[127]
SPIO-ADSCs	n.a.	Superparamagnetic iron oxide NPs	[128]
IONP–MSC–derived NVs	Extracellular nanovesicles	n.a.	[129]
EPCs with magnetic NPs	n.a.	Magnetic NPs	[15]
Embryonic cardiomyocytes with magnetic NPs	n.a.	Magnetic NPs	[130]
IONPs stimulation	IONPs	Chitosan/β-glycerophosphate (CS/GP) hydrogel	[13]
MSC EVs microneedle patches	MSC EVs	Microneedle (MN) patches	[131]
EV-EPCs gel	EPC EVs	Shear-thinning gel	[132]
BMSC-Exo-miR-125b	BMSC-Exo	n.a.	[133]
Control of cardiomyocyte proliferation			
miR-199a-3p NPs hydrogel	miR-199a-3p	DSPE-PEG-Amine and hydrogel	[134]
TT-10 NPs	TT-10	PLGA NPs	[135]
Cell reprogramming			
hiPS-CMs with AuNP-HA-hydrogel	n.a.	AuNP and HA-hydrogel	[136]
hiPS-CMs with PDA-NPs	n.a.	PDA-NPs	[137]
APS-NPs	Ammonium persulfate	Carboxylic gelatin NPs	[138]

Cell-Based Therapies

Recently, mesenchymal stem cells (MSCs)-based therapy has become a promising therapeutic option for MI. Implanted MSCs could reduce the infarct size and mediate cardiac repair through secreting paracrine growth factors for angiogenesis or anti-apoptotic effects. However, the low engraftment rate and the poor survival of the transplanted cells have limited their application. Studies have tried the combination of bioactive nanomaterials with mesenchymal stem cells to increase their survival and improve the efficacy of cardiac repair. Adipose-derived stem cells (ADSCs), as a kind of mesenchymal stem cells, showed several advantages over other stem cells, such as being easily isolated from adipose tissue, rapid proliferation, multipotency, and immunoregulatory properties. In 2017, Herraez and coworkers combined ADSCs with PLGA microparticles (MPs) loaded with neuregulin (NRG) to promote cardiac repair after MI. ADSCs were attached to the surface NRG-PLGA MPs and further coated with collagen and poly-D-lysine. The results showed that NRG-PLGA MPs could enhance ADSC survival in the infarcted myocardium. The combination of NRG-PLGA MPs with ADSCs showed a synergy for increased cell engraftment, a shift to regenerative macrophages, and improved treatment efficacy.[122] In another study in 2017, Hao and coworkers fabricated fullerenol/alginate hydrogel to facilitate ADSC implantation for post-MI therapy. The results showed that the fullerenol/alginate hydrogel could suppress oxidative stress and improve the survival capacity of ADSCs by activating the ERK-p38 signaling pathway under the ROS microenvironment in the infarcted site.[123] In addition, Liu and coworkers reported using alginate hydrogel containing Au@Pt nanoparticles to enhance the therapeutic efficacy of brown adipose stem cells (BASCs) for cardiac repair after MI. Au@Pt nanoparticles displayed excellent antioxidative and conductive properties that significantly enhanced the paracrine capability of BASCs in vitro. Furthermore, Au@Pt/Alg hydrogel loaded with BASCs showed effective antioxidant and anti-inflammatory ability, enhanced the survival of implanted BASCs, and improved electrical conduction velocity and cardiac function, indicating the excellent ability of the hydrogel to promote cardiac repair.[14] In addition, melatonin-loaded PLGA-mPEG nanoparticles,[124] chitosan-silk fibroin hydrogel incorporated with gold nanoparticles,[139] nanoparticles incorporated with ECM/silk proteins,[125] and inverse opals[126] were used to achieve higher ADSC survival rates in the infarcted areas and improve the therapeutic efficacy for MI treatment. In addition, ADSCs could also function as drug-delivery tools. For example, Yokoyama and coworkers explored ADSCs to carry simvastatin-polymer nanoparticles (SimNPs) for cardiac repair. Intravenously injected SimNPs-loaded AdSCs could successfully activate myocardial repair with increased pericardium-derived de novo cardiomyocytes and vascularity.[127]

Some magnetic nanoparticles were used to target the infarcted site under the guidance of an externally applied magnetic field. For example, in 2016, WANG and coworkers used externally fabricated ADSCs preloaded with superparamagnetic iron oxide (SPIO) nanoparticles to enhance the cardiac retention of implanted ASCs with externally applied static magnetic field (SMF). The results showed that externally applied SMF could enhance cardiac retention of implanted SPIO-ADSCs, lead to angiogenesis, decrease CM apoptosis, and enhance heart function recovery after MI.[128] Recently, Lee and coworkers developed magnetic exosome-mimetic extracellular nanovesicles (NVs) from MSCs for better heart diffusion. Briefly, iron oxide nanoparticles (IONPs) are internalized in MSCs, and extracellular nanovesicles (NVs) derived from IONP-MSCs are collected. The results showed that magnetic guidance significantly augmented the retention of IONP–MSC–derived NVs in the infarcted site. Furthermore, IONP–MSC–derived NVs contribute to significantly reduced apoptosis and inflammation and enhanced angiogenesis and cardiac function.[129] Besides MSCs, Zhang and coworkers also used silica-coated magnetic nanoparticles to label endothelial progenitor cells (EPCs) for MI treatment. The results showed that intravenously injected magnetized EPCs could successfully be transplanted into the infarct site with the guidance of an external magnetic field. Meanwhile, magnetized EPCs significantly increased the density of micro-vessels, reduced myocardial apoptosis, and improved cardiac function.[15] Another study by Ottersbach and coworkers reported the exploration of magnetic nanoparticle (MNP) loaded embryonic cardiomyocytes (eCM) and embryonic stem cell-derived cardiomyocytes (ES-CM), respectively, for CM replacement after MI injury. The data revealed that the combination of MNP-loaded cells with magnet application could significantly enhance the engraftment of both eCM and ES-CM, as well as improve left ventricular function.[130] Except for the magnetic guidance function of IONPs to deliver MSC cells to the infarcted site, Bao and coworkers reported using IONPs for precise magnetic stimulation of the vagus nerve for better cardiac repair. Briefly, IONPs are incorporated into

an injectable chitosan/β-glycerophosphate (CS/GP) hydrogel, magnetic field (~100 mT) was used for stimulation. A significantly suppressed inflammation, improved cardiac function, and reduced infarct size were reported after magnetic stimulation, suggesting the promising potential of IONPs-mediated magnetic stimulation for MI therapy.[13]

Except for direct cell therapy, cell-derived factors and exosomes have also been explored for cardiac repair. For instance, Hu and coworkers fabricated microneedle (MN) patches for the delivery of mesenchymal stromal cell-secreted factors (MSCF). Briefly, PLGA nanoparticles loaded with MSCF were located at MN tips made of elastin-like polypeptide gel, while a resolvable HA gel was used as the MN base. The authors demonstrated that MSCF-MN could significantly promote CM proliferation, decrease CM apoptosis, and reduce fibrosis after MI, showing therapeutic potential for cardiac repair.[131] In another study, Chen and coworkers produced shear-thinning gel (STG) containing endothelial progenitor cells derived extracellular vesicles (EVs) to promote cardiac function after MI. EV-STG was shown to efficiently increase peri-infarct vascular proliferation and improve hemodynamic function post-MI.[132] In addition, Chen and coworkers used miR-125b-carried exosomes derived from bone marrow mesenchymal stem cells (BMSC) to alleviate myocardial infarction in rats. BMSC-Exo-miR-125b was found to decrease the apoptotic ratio in I/R myocardium cells, with decreased expression of Bax and caspase-3, and increased expression of bcl-2.[133]

Control of Cardiomyocyte Proliferation

In a study in 2019, Yang and coworkers reported an in vivo miRNA delivery system using a shear-thinning injectable hydrogel for myocardial restoration. MiR-199a-3p was chosen as the model miRNA due to its therapeutic potential for CM proliferation stimulation and cardiac repair. MiR-199a-3p were combined with DSPE-PEG-Amine to form nanoparticles (miNPs) conjugated with cell-penetrating peptides for better CM targeting. The elastin-like protein–hyaluronic acid hydrogels were then used to encapsulate the miNPs. This miNPs-hydrogel system demonstrated significant improvement in cardiac functions with increased ejection fraction by nearly 20%, reduced scar size by 50%, and doubled capillary density in the infarcted site, indicating its potential for myocardial miRNA delivery.[134] Recently, Chen and coworkers developed TT-10-loaded nanoparticles to promote endogenous cardiomyocyte proliferation by targeting the Hippo/Yes-associated protein (Hippo/Yap) pathway. By encapsulating TT-10, an activator of the Hippo pathway, into PLGA nanoparticles, TT-10 NPs were fabricated. The authors demonstrated that TT-10 NP treatment leads to significantly smaller infarct size and improved cardiac function, as well as increased CM proliferation and decreased CM apoptosis.[135]

Cell Reprogramming

Human-induced pluripotent stem cells (hiPS)-derived cardiomyocytes have emerged as a potential way to substitute the infarcted myocardium for cardiac repair after MI; still, the immature phenotype of hiPS-CMs and the limited contractile output pose an obstacle to its application. Various nanomaterials have been applied to try to overcome these limitations.[140] For instance, in 2021, Li and coworkers explored the possibility of a hybrid gold nanoparticle-HA hydrogel to enhance the function of engrafted hiPS-CMs after MI. The authors showed that transplanted AuNP-HA-hydrogel containing hiPS-CMs developed more robust gap junctions and exerted stronger angiogenic effects for better cardiac recovery.[136] Similarly, Alvi and coworkers demonstrated the application of polydopamine nanoparticles (PDA-NPs) to enhance the contractility and beat propagation of hiPS-CMs. The results showed that PDA-NPs-treated hiPSC-CMs demonstrated increased calcium cycling, enhanced contractility, and electrical conductivity, showing the potential for cardiac modulation.[137] Recently, Song and coworkers constructed ammonium persulfate (APS) loaded carboxylic gelatin−methacrylate nanoparticles for cardiac repair after MI through epicardial epithelial−mesenchymal transition. APS-NPs demonstrated good performance by transforming Wilms tumor 1-positive (WT1+) epicardial cells into endothelial-like cells. More interestingly, APS-NPs significantly improved cardiac function for MI in vivo, showing a great potential in the repair of MI.[138] In general, however, these approaches targeting cardiac repair have modest effects due to the difficulty of cardiac regeneration, especially for adult cardiomyocytes. Most of the aforementioned studies are still in their preliminary stages, necessitating further evaluation of survival rates and the duration of efficacy following transplantation.

Summary and Future Prospect

Myocardial infarction is a severe heart disease with high mortality, which accounts for nearly 75% of sudden cardiac death. Recently, the development of nanomaterials has led to encouraging results for improving the efficacy of myocardial infarction therapy. This review provides a systematic review of recent progress in nanomedicines for MI therapy from 2016 to 2023, hoping to provide useful information for researchers who work in designing nanomedicines for MI therapy. The therapeutic mechanism for those nanomedicines could be divided into anti-cardiomyocyte death, enhancing angiogenesis, promoting ROS clearance, inflammation modulation, inhibiting cardiac remodeling, and promoting cardiac repair. Although much progress has been made in the field, few nanomedicines have been approved in clinics for MI treatment.

One challenge is the low targeted efficiency and drug retention in the myocardium although combined with nanomaterials. Studies are required for stable and efficient NP production, improved drug encapsulation efficiency, and higher targeting effects. Furthermore, the unique design of each nanomedicine makes it difficult to evaluate the cardiac repair effect among similar studies and for further pre-clinical trials. Also, animal models used for those reported pre-clinical experiments are mainly mice and rats, but rarely pigs, still a long way to clinical trials. Another challenge that blunts their application is the administration way. Due to the special structure of the beating heart, intramyocardial injection is still the most commonly used way for efficient and targeted drug delivery, however, the following puncture injury limited their application significantly. In addition, the application of nanomedicines faces systemic toxicity issues. There is a consensus on the good biocompatibility of liposomes or some polymers, however, the toxicity of some metal nanomedicines has been widely reported, and this may limit their clinical application in the future. Besides, as a novel non-viral choice for MI therapy, the application of nucleic acid drugs such as plasmids, miRNAs, and siRNAs is also limited by their potential for immunoreactivity and gene editing in non-target organs. For the off-target effects of nanomedicines, nano-systems responded to external stimuli such as light, electricity, and magnetism could alleviate off-target effects; however, few studies applied this system in MI therapy. At present, we also notice that although various nanomedicines such as miRNAs, siRNA, classical drugs, and traditional Chinese medicines have been explored, the detailed mechanism of their effects especially for certain miRNAs and some traditional Chinese medicines are not clear. Examining the specific signaling pathway that regulates a certain process is key for improved efficacy and further application. Meanwhile, the complexity of MI poses a challenge to treatment strategies, how to combine these strategies to achieve better curative effects is critical. Besides, nanomedicines that target new mechanisms are needed. For instance, in the part of the anti-cardiomyocyte death strategy, most nanomedicines target apoptosis and necrosis but not recently discovered ferroptosis and pyroptosis. Overall, the breakthrough of nanomedicines for MI therapy calls for both advanced targeted nanocarriers and newly discovered mechanism targets.

Abbreviations

ADSCs, adipose-derived stem cells; AMO-1, anti-miR-1 antisense oligonucleotide; APS, ammonium persulfate; Bcl-2, B-cell lymphoma-2; bFGF, basic fibroblast growth factor; BMDM, bone marrow-derived macrophage; BMSC, bone marrow mesenchymal stem cells; CLPs, cationic liposomes; CM, cardiomyocytes; CMC, carboxymethylcellulose; CsA, Cyclosporin A; cTnT, anti-cardiac troponin T; DCs, dendritic cells; ECM, extracellular matrix; EMMPRIN, extracellular matrix metalloproteinase inducer; EPCs, endothelial progenitor cells; ETC, mitochondrial electron transport chain; EVs, extracellular vesicles; GCD, gadolinium-doped carbon dots; GSH, glutathione; GST, glutathione-S-transferase; HA, hyaluronic acid; hiPS, human-induced pluripotent stem cells; ICA, icariin; IL, interleukin; IONPs, iron oxide nanoparticles; LPS, lipopolysaccharide; LV, left ventricular; Mdivi 1, mitochondrial division inhibitor 1; MI, myocardial infarction; miR, microRNA; MMP-2, matrix metalloproteinase-2; mPTP, mitochondrial permeability transition pore; MRI, magnetic resonance imaging; MSC, mesenchymal stem cell; MSCF, mesenchymal stromal cell-secreted factors; MSN, mesoporous silica nanoparticles; MTX, methotrexate; NHDFs, normal human dermal fibroblasts; NP, nanoparticle; NOXs, NADPH oxidase family; PAMAM-His, poly(amidoamine)-histidine; PBA, phenylboronic acid; PCL, poly-ε-caprolactone; PDA, Polydopamine; PDCD4, programmed cell death 4; PDGF, platelet-derived growth factor; PEG, polyethylene glycol; PEI, polyethyleneimine; PGA, polyglutamic acid; PKCε, protein kinase C ε; PLA, polylactic acid;

PPARγ, peroxisome proliferator-activated receptor γ; PTEN, gene of phosphate and tension homology deleted on chromosome ten; PVP, polyvinylpyrrolidone; RGD, arginine-glycine-aspartic acid tripeptide; RSV, ROS scavenger resveratrol; SaB, salvianolic acid B; SDF-1α, stromal cell-derived factor 1-alpha; SMF, static magnetic field; SOD1, superoxide dismutase 1; Tβ4, thymosin β4; TCA, tricarboxylic acid; TLR4, Toll-like receptor 4; TNF-a, tumor necrosis factor-a; Tregs, regulatory T cells; VA, vanillyl alcohol; VEGF, vascular endothelial growth factors.

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Disclosure

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