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REVIEW

Nanoparticles: Promising Tools for the Treatment and Prevention of Myocardial Infarction

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Abstract: Despite several recent advances, current therapy and prevention strategies for myocardial infarction are far from satisfactory, owing to limitations in their applicability and treatment effects. Nanoparticles (NPs) enable the targeted and stable delivery of therapeutic compounds, enhance tissue engineering processes, and regulate the behaviour of transplants such as stem cells. Thus, NPs may be more effective than other mechanisms, and may minimize potential adverse effects. This review provides evidence for the view that function-oriented systems are more practical than traditional material-based systems; it also summarizes the latest advances in NP-based strategies for the treatment and prevention of myocardial infarction.

Keywords: nanoparticles, myocardial infarction, treatment, prevention

Introduction

The growing burden of ischemic heart disease (IHD) is a major public health issue. The most harmful type of IHD is acute myocardial infarction (MI), which leads to loss of tissue and impaired cardiac performance, accounting for two in five deaths in China.[1] Timely revascularization after MI, including percutaneous coronary intervention, thrombolytic treatment and bypass surgery, is key to improving cardiac function and preventing post-infarction pathophysiological remodeling.[2] However, these effective but invasive approaches cannot be used in all patients owing to their applicability, which is limited based on specific clinical characteristics, and the possibility of severe complications such as bleeding and reperfusion injury.[2,3] Attempts to limit infarct size and improve prognosis using pharmacotherapy (including antiplatelet and antiarrhythmic drugs and angiotensin-converting enzyme inhibitors) without reperfusion has been proven generally inefficient, due to non-targeted drug distribution and side effects, and short half-life of some drugs.[1,3,4] Consequently, many patients in which this approach is used still progress to cardiac hypertrophy and heart failure.[1] Growth and rupture of atherosclerotic plaques and the ensuing thrombosis are the major causes of acute MI.[4] Currently available interventions for atherosclerosis (AS) including statins can reduce acute MI, but the effects vary between individuals, and leave significant residual risks.[5–8] Some chemotherapies, such as docetaxel[9] and methotrexate,[10,11] also seem to have beneficial effects in AS; however, systemic administration of these drugs is limited because of their adverse effects.[12] The demand for safer and more efficient therapies and prevention strategies for MI is therefore increasing.

Several optimized strategies have so far been explored, one of which is the application of nanoparticles (NPs). These nanoscale particles have been widely

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used in the treatment of tumors and neural diseases.[13,14] NPs enable delivery of therapeutic compounds to target sites with high spatial and temporal resolution, enhancement of tissue engineering processes and regulation of the behaviour of transplants such as stem cells. The application of NPs improves the therapeutic effects and minimizes the adverse effects of traditional or novel therapies, increasing the likelihood that they can be successfully translated to clinical settings.[15–18] However, research on NPs in this field is still in its infancy.[5,19–21] This review summarizes the latest NP-based strategies for managing acute MI, mostly published within the past 7 years, with a particular focus on effects and mechanisms rather than particle types, which have been extensively covered in other reviews (Figure 1). In addition, we offer an initial viewpoint on the value of function-based systems over those based on materials, and discuss future prospects in this field.

The Types and Properties of Nanoparticles

The Types of Nanoparticles

A multitude of NP types are currently under investigation, including lipid-based NPs, polymeric NPs, micelles, inorganic NPs, and exosomes. Virus can also be considered as NPs; however they will not be discussed in this review.[22]

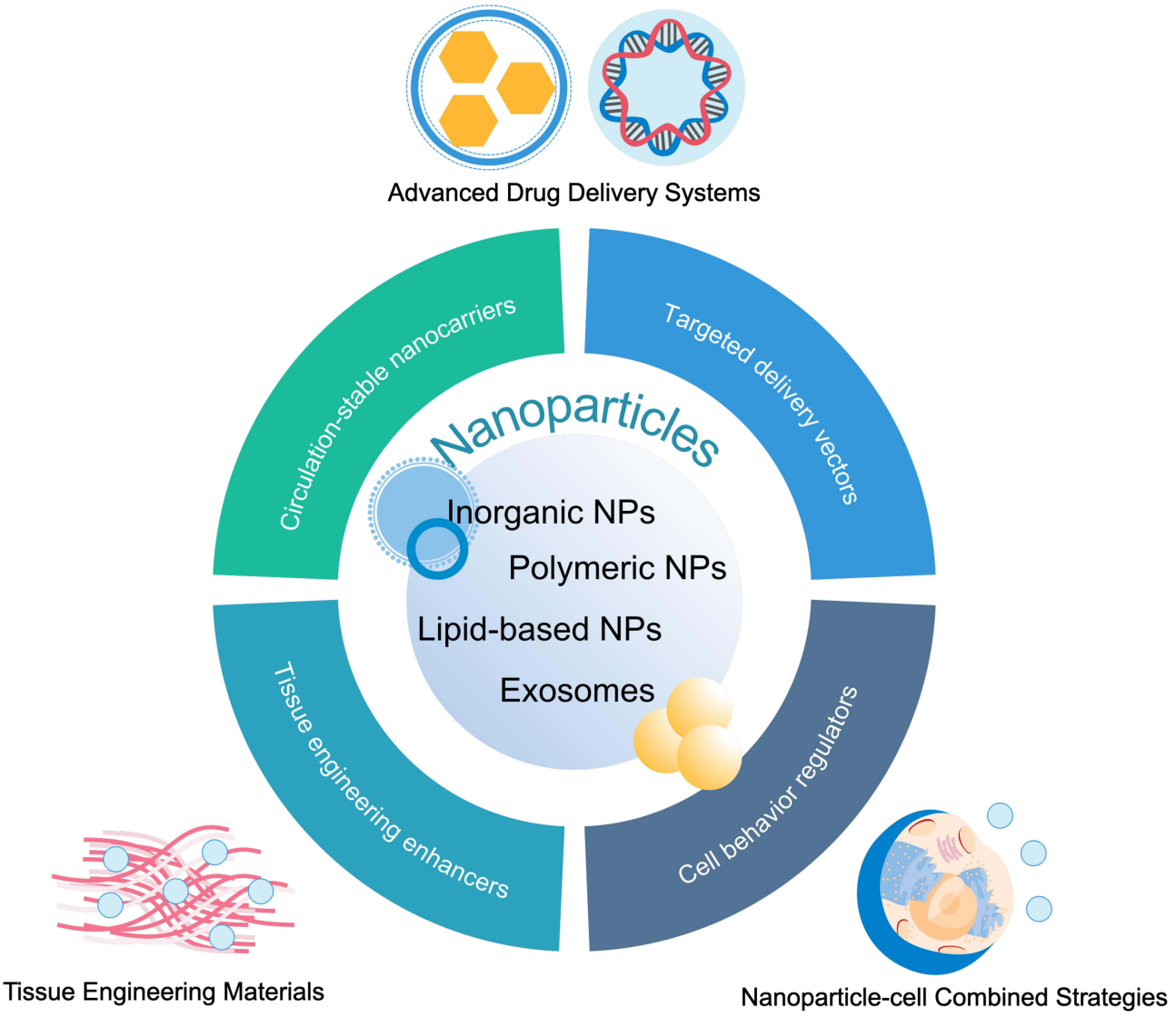

Figure 1 Overview of nanoparticle-based strategies for the treatment and prevention of myocardial infarction. Nanoparticles are capable of delivering therapeutic agents and nucleic acids in a stable and targeted manner, improving the properties of tissue engineering scaffolds, labeling transplanted cells and regulating cell behaviors, thus promoting the cardioprotective effects of traditional or novel therapies.

NPs made from different materials show similar in vivo metabolic kinetic characteristics and protective effects on infarcted heart.[19,20] Function-based NP types, oriented towards a specific purpose, may be preferable compared with traditional types, on account of their practicality in basic research and clinical translation. In this review, we discuss NPs used in the treatment and prevention of MI that fall into the following four categories: 1) circulation-stable nanocarriers (polymeric, lipid or inorganic particles); 2) targeted delivery vectors (magnetic or particles modified to improve target specificity); 3) enhancers of tissue engineering; and 4) regulators of cell behavior (Figure 1). We propose that the choice of each NP for any given application should be primarily based on the roles or mechanisms they perform.

Many NPs, whether composed of either naturally occurring or synthetic materials, act as nanocarriers to improve the circulating stability of therapeutic agents.[15,16] Polymeric NPs comprise one of the most widely employed types, with excellent biocompatibility, tunable mechanical properties, and the ability be easily modified with therapeutic agents using a broad range of chemical techniques.[23,24] The most commonly used polymer for these NPs is polylactide-co-glycolide (PLGA), which has Food and Drug Administration approval.[25,26] Recently, there has been a therapeutic emphasis on polydopamine (PDA), from which several related nanomaterials have been created, including PDA NPs and PDA NP-knotted hydrogels.[27,28] NPs made from polylactic acid (PLA),[29,30] poly-ε-caprolactone (PCL),[31] polyoxalates,[32] polyacrylonitrile,[33] chitosan[29,34] and hollow mesoporous organosilica[35] have also been constructed and administered in vitro in cells and in vivo in animal models.

Lipid NPs or liposomes are also considered promising candidates for the delivery of therapeutic agents, due to their morphology, which is similar to that of cellular membranes and ability to carry both lipophilic and hydrophilic drugs. These non-toxic, non-immunogenic and biodegradable amphipathic nanocarriers can be designed to reduce capture by reticuloendothelial cells, increase circulation time, and achieve satisfactory targeting.[36,37] Solid lipid NPs (SLNs) combine the advantages of polymeric NPs, fat emulsions, and liposomes, remaining in a solid state at room temperature. Active key components of SLNs are mainly physiological lipids, dispersed in aqueous solution containing a stabilizer (surfactant).[38] Micelles are made by colloidal aggregation in a solution through self-assembly of amphiphilic polymers, or a simple lipidic layer of transfer vehicles;[39] these have been used in cellular and molecular imaging[40] and treatment[41] for a long time.

Inorganic NPs used in basic IHD research are classified as metal, metal compounds, carbon,[42] or silicon NPs;[43] these are relatively inert, stable, and biocompatible. Gold (Au),[44] silver (Ag)[45] and copper (Cu)[46] are commonly used materials in their production. These NPs can be delivered orally,[47] or injected intravenously[48] or intraperitoneally.[56] However, they are more widely used to construct electrically conductive myocardial scaffolds in tissue engineering.[49,50] Myocardial patches and scaffolds are promising therapeutic approaches to repairing heart tissue after IHD; incorporating conductive NPs can further improve functionality, introducing beneficial physical properties and electroconductivity. Some organic particles, such as liposomes anchored with poly(N-isopropylacrylamide)-based copolymer groups, are also suitable for the production of effective nanogels or patches for this purpose.[37]

Several metal compounds have been used for treatment of IHD.[51–54] The application of magnetic particles made from iron oxide has been of particular interest in recent research. These NPs are more prone to manipulation with an external magnetic field, and thus serve as powerful tools for targeted delivery of therapeutics. In addition, modification with targeted peptides or antibodies is another approach to the construction of targeted delivery systems.

Another strategy to protect cardiac performance after MI is the transplantation of cells; however, the beneficial effects of this are currently limited.[58] Many NPs can improve the behavior of cells; in this context, they may stimulate cardioprotective potential. In particular, exosomes – a major subgroup of extracellular vesicles (EVs) with a diameter of 30–150 nm, which are secreted via exocytosis[55] – represent novel, heterogeneous, biological NPs with an endogenous origin. They are able to carry a variety of proteins, lipids, nucleic acids, and other bioactive substances.[55–57] Mechanistic studies have confirmed that exosomes offer a cell-free strategy to rescue ischemic cardiomyocytes (CMs).[59,60]

The Physical Properties and Modifications of Nanoparticles

The physical properties of NPs, including size, shape, and surface charge, impact on how biological processes behave, and consequently, responses in the body.[61] The recommended definition of NPs in pharmaceutical technology

and biomedicine includes a limitation that more than 50% of particles should be in a size distribution range of 10–100 nm.[39] However, this is not strictly distinguished in studies, so for the purposes of this review, we have relaxed this definition. Small NPs have a faster uptake and processing speed and longer blood circulation half-lives than larger ones; a decreased surface area results in increased reactivity to the microenvironment and greater speed of release of the compounds they carry.[61–63] However, an exception to this principle is that, among particles of less than 50 nm diameter, larger NPs have longer circulatory half-lives.[64,65] NPs can be spherical, discoidal, tubular or dendritic.[61,63] The impact of NP shape on uptake and clearance has also been revealed;[66,67] for instance, spheres endocytose more easily,[20] while micelles and filomicelles target aortic macrophages, B cells, and natural killer (NK) cells in the immune system more effectively than polymersomes.[68] In terms of charge, cationic NPs are more likely to interact with cells than negatively charged or neutral particles because the mammalian cell membrane is negatively charged.[62] As a result, positively charged particles are reported to be more likely to destabilize blood cell membranes and cause cell lysis.[61] Additionally, the rate of drug release is largely determined by the diameter of the pore. Motivated by the idea, Palma-Chavez et al developed a multistage delivery system by encapsulating PLGA NPs in micron-sized PLGA outer shells.[69]

Some types of NPs, such as micelles, possess core–shell morphological structures: a core composed of hydrophobic block segments is surrounded by hydrophilic polymer blocks in a shell that stabilizes the entire micelle. The core provides enough space to accommodate compounds, while the shell protects drug molecules from hydrolysis and enzymatic degradation.[36] Surface chemical composition largely governs the chemical interactions between NPs and molecules in the body. Appropriate surface coatings can create a defensive layer, protect encapsulated cargo, and affect biological behaviors. Coating with inert polymers like polyethylene glycol (PEG) is the most commonly used method, which hinders interactions with proteins, alters the composition of the protein corona, attenuate NP recognition by opsonins which tag particles for phagocytosis, and extend the half-life of particles.[36,70] Additionally, PEG coating helps the therapeutic agents reach ischemic sites, because PEGylated macromolecules tend to diffuse in the interstitial space of the heart.[71] Functionalization of gangliosides can further attenuate the immunogenicity of PEGylated liposomes without damaging therapeutic efficacy.[72] Removal of detachable PEG conjugates in the microenvironment of the target sites improves capture by cells. Wang and colleagues synthesized PDA-coated tanshinone IIA NPs by spontaneous hydrophobic self-assembly.[73] Polyethyleneimine (PEI) is capable of condensing nucleic acid and overcoming hamper of cell membrane. Therefore, modification with PEI is mainly used for the transport of DNA and RNA.[74] Of note, despite their inertness, novel NPs composed of metals can also be modified with compounds such as PEG, thiols, and disulfides.[48,75] Hydrogels mixed with peptide-coated Au NPs attain greater viscosity than hydrogels mixed with Au NPs.[24]

Targeted delivery is a primary goal in the development of nanocarriers. Passive targeting is based on enhanced permeability in ischemic heart tissue, which does not meet the needs of clinical application.[76] This fact has prompted work on targeting agent modification and magnetic guidance. Conjugation with specific monoclonal antibodies is a feasible method for delivering drug payloads targeted to ischemic lesions. Copper sulfide (CuS) NPs coupled to antibodies targeting transient receptor potential vanilloid subfamily 1 (TRPV1), permit specific binding to vascular smooth muscle cells (SMCs), and can also act as a switch for photothermal activation of TRPV1 signaling.[52] In another study conducted by Liu and colleagues, two types of antibodies, binding CD63 (expressed on the surface of exosomes) or myosin light chain (MLC, expressed on injured CMs) are utilized to allow NPs to capture exosomes and accumulate in ischemic heart tissue. These NPs have a unique structure comprising an ferroferric oxide core and PEG-decorated silica shell, which simultaneously enables magnetic manipulation and molecule conjugation via hydrazone bonds.[21] Targeted peptides such as atrial natriuretic peptide (ANP),[43] S2P peptide (plague-targeting peptide),[77] and stearyl mannose (type 2 macrophage-targeting ligand)[16] allow NPs to precisely target atherosclerotic tissue and ischemic heart lesions. Modification with EMMPRIN-binding peptide (AP9) has been shown to enable more rapid uptake of micelles by H9C2 myoblasts and primary CMs and to deliver drug payloads targeted to lesions in vivo.[78,79] Another strategy for targeted nanocarriers is to produce cell mimetic carriers. Using the inflammatory response as a marker after MI,[76] Boada and colleagues synthesized biomimetic NPs (leukosomes) by integrating membrane proteins purified from activated J774 macrophages into the phospholipid bilayer of NPs. Local chronic inflammatory lesions

demonstrated overexpression of adhesion molecules, which bound leukosomes efficiently.[80]

The Biocompatibility of Nanoparticles

The biocompatibility of NPs is difficult to predict because any interaction with molecules or cells can cause toxic effects. Generally, NPs remain in blood, but can also extravasate from vasculature with enhanced permeability, or accumulate in the mononuclear phagocyte system.[81] Important causes of NP-associated toxicity include: oxidative stress injury and cell apoptosis secondary to the production of free radicals, lack of anti-oxidants, phagocytic cell responses, and the composition of some types of particles.[61] Hepatotoxicity, nephrotoxicity and any other potential off-target organ damage caused by accumulation of particles, especially those with poor degradability and slow clearance, are also essential to explore in toxicity tests.[82] Additionally, the evaluation of evoked immune responses according to the expression of inflammatory factors and stimulation of leukocytes in cell lines and animal models is also important.[83]

A few studies have reported NP-associated acute and chronic hazards in pharmacological applications, although some of these observations may be contentious. Specifically, aggregation of non-functionalized carbon nanotubes (CNTs) has been observed owing to inherent hydrophobicity of these particles.[61] Aside from inflammation and T lymphocyte apoptosis, multi-walled CNTs can rupture cell membranes, resulting in macrophage cytotoxic effects.[84,85] Silica NPs induce vascular endothelial dysfunction and promoted the release of proinflammatory and procoagulant factors, mediated by miR-451a negative regulation of the interleukin 6 receptor/signal transducer and activator of transcription/transcription factor (IL6R/STAT/TF) signaling pathway.[86–88] Metal NPs, such as Au and Ag, can also penetrate the cell membrane, increase oxidative stress and decrease cell viability.[89,90] Consequently, exposure to Au may cause nephrotoxicity[91] and reversible cardiac hypertrophy.[92] El-Hussainy and colleagues observed myocardial dysfunction in rats given alumina NPs.[93,94] Nemmar and colleagues investigated the toxicity of ultrasmall superparamagnetic iron oxide nanoparticles (SPIONs) administered intravenously, which resulted in cardiac oxidative stress and DNA damage as well as thrombosis.[95] Cell-derived exosomes and a majority of natural polymers are considered relatively safe;[83] however, Babiker and colleagues demonstrated that dendritic polyamidoamine NPs compromise recovery from ischemia/reperfusion (I/R) injury in isolated rat hearts.[96] The effects of degradation byproducts are also of concern.[83] An advantage of the nanoscale size of NPs is that their injection is unlikely to block the microvascular system; however, it remains controversial whether NPs give rise to arrhythmias.[97] These factors highlight that examining the biocompatibility of NPs both in vitro and in vivo is a vital component of preclinical or clinical research.

NP toxicity depends on many parameters, including material composition, coating, size, shape, surface charges and concentration.[39] For instance, larger particles seem to be more favorable from a toxicology standpoint.[83] However, single-walled CNTs are considered more harmful than multi-walled CNTs, due to their smaller size resulting in less aggregation and increased uptake by macrophages.[61] Cationic AuNPs are more toxic compared with anionic AuNPs, which appear to be nontoxic.[98] Generally speaking, NP-associated toxicity can be lowered by functionalization with nontoxic surface molecules, stabilization and localization in the region of interest by using scaffolds.[24,99] The toxicity of CNTs mediated by oxidative stress and inflammation was reduced using these strategies in several studies.[24,100] Local application and targeted delivery also enabled dose reduction and concurrently decreased the incidence of adverse effects. Administration of therapeutic agents directly into the infarcted or peri-infarcted myocardium is a conventional approach with a low risk of inducing embolization.

The Advanced Nanotherapeutic Strategies for Myocardial Infarction

The Advanced Drug Delivery Nanocarriers

NP is a suitable method for the administration of therapeutic agents in terms of the minimization of side effects, enhanced stability of cargo, and possibility of controlled delivery and release.[76] Detailed information on the experimental design and results of the latest studies on the use of NPs as therapeutic vectors are provided in Table 1. Recently, several drugs approved for clinical use as immunosuppressants have been suggested as potentially effective cardioprotective agents. For example, NPs containing cyclosporine A inhibited apoptosis and inflammation in ischemic myocardium by improving mitochondrial function.[25,101] Commercial methotrexate also showed minor cardioprotective effects; additionally, when loaded into lipid core NPs, adenosine bioavailability and echocardiographic and morphometric results were all improved

Table 1 NPs-Based Drug Delivery Systems for Treatment for MI Reported in the Last 7 Years

Material	Modification Method	Particle Size	Payload	Species and Model	Cardiac Therapeutic Effects and Assessment Method				Safety	Ref.
					Function and Hemodynamy	Necrosis and Fibrosis	Angiogenesis	Other Effects		
Delivery of western drugs										
PLGA	Modification with SS31 (a mitochondria-targeted peptide) and PEGylation	~54 nm	CsA	Rats; I/R (LAD for 30 min)	Recovery of heart rate and ± dp/dtmax↑	Infarct size↓(Evans Blue/TTC dual staining);	↑(IF)	Recovery of ΔΨm; production of mitochondrial ROS and apoptosis of H/R injured H9c2 cells↓; serum myocardial damage biomarker↓; better mitochondrial morphology		[25]
Soybean phosphatidylcholine and glycyrrhizinic acid salts		110±3nm	Celecoxib	Mice; LAD	LVEF, FS↑; expansion of chamber dimensions, LVEDV and LVESV↓ (E)	LV wall thinning and lumen dilatation↓ (HE staining)	↑(IHC)		No associated thrombotic events	[103]
Liposome		~60 nm	Methotrexate	Rats; LCA	LVIDD, LVISD and cardiac hypertrophy↓; EF↑(E)	Infarct size↓; cardiomyocyte hypertrophy↓; Collagen I/III↓(HE and Masson's trichrome)		Inflammatory cells↓; ROS↓; expression of VEGF and adenosine receptors↑; cell death in the non-infarcted↓ (HE, IF); apoptosis↓(Western blot)	No clinical or laboratory toxicity in the animals	[102]
PLGA		~271nm	Pioglitazone	Mice and mini-pig; I/R (LAD for 30min/1h)	LVEDD, LVESD↓(E)	Infarct size, reperfused infarct size, and fibrosis↓(Masson's trichrome)		Activity of cathepsin B↓; Ly6Clow monocytes and type 1 macrophages↓; type 2 macrophages, myocardium PPARγ DNA-binding activity↑; mortality↓;		[104]

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Poly-lysine-PEG copolymer		~77nm	Exenatide	Rats; I/R (LAD for 30min)	LVEF, +dp/dtmax, and BP↑, LVEDP and HR↓(E, non-invasive BP Analyzer)	Histopathological alterations↓(HE)		Serum CK, LDH, and cTnT↓, GLP-1↑; cardial SOD and GLP-1 receptor↑, malondialdehyde↓;		[106]
PLGA		~159nm	Pitavastatin	minipigs, I/R (ligation of left circumflex coronary artery for 60min)	LVEF and FS↑ (E) LVESV↓(E)	↓(Masson-Trichrome)		Inhibition of monocyte/macrophages		[107]
PLGA		~200nm	Irbesartan	Mice; I/R (LAD for 30min)	LVEF,LVFS↑(E)			Inflammatory protease activity and Ly6C high monocytes recruitment↓		[187]
PEG-carboxymethyl chitosan		~68 nm	Insulin	Diabetes rats (induced by streptozotocin); I/R (LAD for 45min)		↓(TTC)		CK, LDH↓; NF-κB, SSAT↓, ODC↑		[188]
PEG-PLA	Conjugation with fibrin-targeting moiety clot-binding peptide (cys-arg-glu-lys-ala)	121.4±2.6 nm	Thymosin beta 4	Mice; I/R (LAD for 90min)	LVEDD, LVESD↓(E)		↑(IF)	Wt-1↑; CMs apoptosis↓	No toxicity	[189]
Delivery of plant-derived therapeutic agents (traditional Chinese medicine)										
mPEG-PLA-TPGS		100–200nm	Tanshinone IIA	Mice; LAD	LVEDD, LVESD↓, LVEF, FS↑(E)	Heart weight to body weight ratio, scar circumference and fibrosis area↓(Masson's trichrome)		Myocardial angiotensin II type 1 receptor, nuclear NF-κB p65, TNFα, TGFβ1, SMAD3, MMP-2, MMP-9, IL-1β, IL-6, MCP1 and IL-18 expression and apoptosis↓		[30]

(*Continued*)

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Table 1 (Continued).

Material	Modification Method	Particle Size	Payload	Species and Model	Cardiac Therapeutic Effects and Assessment Method				Safety	Ref.
					Function and Hemodynamy	Necrosis and Fibrosis	Angiogenesis	Other Effects		
Au		203.4 ± 4.72nm	Pe.EA	Mice; ISO-induced MI		Cardial necrosis and separation of myocardial fibers↓		Serum levels of TG, TC, LDL, ALT, AST, LDH and CPK↓; DNA damage↓		[50]
PLGA	Coating with PEG modified by IMTP, as well as SS-31 peptide (targeting to mitochondria)	~89nm	Resveratrol	H9c2 cell (hypoxia) Rats; I/R (LAD for 30min)	±dp/dtmax and LVESP ↑(E)	Infarct size↓(TTC)		LDH↓; uptake↑; ROS↓		[108]
SLNs	PEGylation and arginine-glycine asparagine modification	~110nm	Puerarin	Rats; LAD		Infarct size↓(TTC)				[109]
MSNs		100–150nm	Quercetin	Rats; I/R (LAD)	↑(E)	Infarct size↓(Masson's trichrome)		Apoptosis and oxidative stress↓		[110]
Polymer		30–100nm	Curcumin	Rats; ISO-induced MI		Myocardial necrosis↓(HE staining)		CK, CK-MB, oxidative stress markers↓; serum levels of MMP2, MMP9, TNF-α, IL-6, IL-1α, IL-1β, MCP-1, and RANTES↓, local inflammation↓		[111]
PLGA		~194.82nm	Wogonin	Rats; ISO-induced MI		Infarct size edema, and necrosis↓(TTC, HE)		LDH, cTnT, and CK-MB, lipid peroxidation product, TNF-α, IL-1β, and IL-6↓; catalase, SOD, Nrf2 and heme oxygenase-1↑; myocardial inflammatory cells↓		[190]
Lipid NPs	PEGylation	~83.9 nm	Baicalin	Rats; LAD		Infarct size↓(staining/ photographed)				[191]

Lipid-polymer hybrid NPs	Conjugation with distearoyl phosphatidylethanolamine-PEG	100–200nm	Salvianolic acid B and panax notoginsenoside	Rats; I/R (LAD for 45min)		Infarct size↓(TTC)			No toxicity	[192]
SLNs	Modification with PEG and MMP-targeting peptide	~130nm	Schisandrin B	Rats; partial LCA		Infarct size↓(TTC)				[193]
SLNs		~104.83nm	Flavonoid extract from *Dracocephalum moldavica L.*	Rats; I/R (LAD for 30min)		Infarct size↓(TTC); histopathological damage↓(HE)		Expression of LDH, CK, IL-1β and TNF-α↓, integrity of the myocardial membrane and myocardial fibers↑		[194]
Au		17–29 nm	Pro-anthocyanidin	Rats; ISO-induced myocardial injury				AST, ALT, cTnT and homocysteine in plasma↓		[195]
Delivery of small molecular inhibitors										
Porous silicon	Functionalization with ANP	~180nm (Ref. 113)	3i-1000; OR C143 (a ERK1/2 inhibitor)	Rats; ISO-induced MI				ANP, BNP, COL1A1, IL-6 and OPN gene expressions↓; Hypertrophic signaling↓ (ERK signaling cascade)		[43, [113]
PLGA		~227nm	TAK-242	Mice; I/R (LAD for 30min)	LVEDD, LVESD↓(E)	Infarct size↓(Masson's trichrome)		HMGB1,NF-κB↓; Neutrophils and Ly-6C high inflammatory monocytes↓		[112]
Poly (N-isopropylacrylamide) and N,N′-methylenebis (acrylamide)		~244 nm	Y-27632 and t-PA	Rats; I/R (LAD for 30min)	LVEF, FS↑(E)	Infarct size↓(Masson's trichrome)		α-SMA level, cellular contractility, reduce stress fiber formation, and decrease CTGF expression↓		[196]
PLGA		~194nm	Mdivi1	Mice heart (Langendorff-Perfused); I/R (ischemia for 45min)		Infarct size↓				[197]

(*Continued*)

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Table 1 (Continued).

Material	Modification Method	Particle Size	Payload	Species and Model	Cardiac Therapeutic Effects and Assessment Method				Safety	Ref.
					Function and Hemodynamy	Necrosis and Fibrosis	Angiogenesis	Other Effects		
Delivery of growth factor and other regulatory molecules										
PLGA; OR Crosslinked heparin polysaccharide		113.1 ± 5.2 nm (PLGA); OR 150–155nm (Heparin: VEGF 100:6)	VEGF	Mice; LAD	LVEF, LVFS, LVEDD and LVESD↑(E); LVIDD, LVISD↓(E)	Infarct size↓, wall thicknesses↑ (Sirius red and fast green staining)	↑(IHC)	Myocardiac water content↓; lymphangiogenesis↑; heart-to-body weight ratio and heart weight-to-tibia length ratio↓	No obvious toxicity in vivo	[26, 114]
Chitosan and fucoidan		<150 nm	VEGF or SDF-1	Rats; LAD	LVEF, SF↑(E)	Infarct size ↓(Masson's trichrome)	↑(IF)	CMs proliferation↑(IF);		[115]
Gelatin NPs		180–255 nm	BIO and IGF-1	Rats; LAD	LVEF, FS↑; LVEDD, LVESD↓ (E)	CMs↑(HE)	↑(IHC)			[117]
Poly(ethylene argininylaspartate diglyceride)			TIMP-3/ FGF-2/ SDF-1α	Rats; LAD	FAC↑, LVESV, LVEDV↓(E)		↑(IF)	Preserved myocardial elasticity (MRI); CMs survival↑; apoptosis↓(IF); inflammatory↓		[118]
Delivery of other payloads										
Polystyrene coated with iron oxide		230±35nm	Diallyl trisulfide (H2S donor compound)	Mice; I/R (LAD for 30min)	HR↓; EF, FS↑(E)				No detrimental effect on homeostasis in vivo at appropriate concentration	[15]
Au		14±3 nm	DNAzyme	Rats; LAD	±dp/dt, LVEF, FS↑(E)			TNF-α mRNA↓(qPCR)		[119]

PEG-poly oxymethyl estyrene		~40nm	2,2,6,6-tetramethyl piperidine-1-oxyl	Dog; I/R (LAD for 90min)	Infarct size↓(TTC)			Apoptosis↓; ventricular fibrillation ↓; coronary venous end-products of nitric oxide↓	[198]
Dodecafluoropentane		~250nm	Oxygen	Mice; LAD		Infarct size↓(TTC)			[199]
Lipid NPs	Modification with ANP	167.9 ±4.6nm	Adenosine prodrug	Rats; I/R (LAD for 45 min)		Infarct size↓(TTC)			[200]

Abbreviations: PLGA, poly(lactic-co-glycolic acid); NPs, nanoparticles; PEG, poly (ethylene glycol); i.v., intravenous injection; CsA, cyclosporine A; I/R, ischemia/reperfusion; LAD, left anterior descending ligation; ±dp/dtmax, the maximal rate of the increase (decrease) of LV pressure; TTC, triphenyltetrazolium chloride; If, immunofluorescence; ΔΨm, the membrane potential; ROS, reactive oxygen species; LV, left ventricular; EF, ejection fraction; FS, fractional shortening; ESV, end-systolic volume; EDV, end-diastolic volume; E, echocardiography; IHC, immunohistochemical staining; TEM, transmission electron microscope; LCA, left coronary artery ligation; LVISD, systolic LV internal diameter; LVIDD, diastolic LV internal diameter; PPAR, peroxisome proliferators-activated receptors; ESP, end systolic pressure; EDP, end diastolic pressure; BP, blood pressure; GLP, glucagon-like peptide; SOD, superoxide dismutase; SSAT, spermidine/spermine N¹-acetyltransferase; ODC, ornithine decarboxylase; PLA, polylactide acid; TPGS, D-α-Tocopheryl PEG 1000 succinate; MMP, matrix metalloproteinase; MCP, monocyte chemoattractant protein; ISO, isoprenaline; Pe.EA, ethyl acetate fraction of Paeonia emodi; CPK, creatine phosphokinase; IMTP, ischemic myocardium targeted peptide; MSNs, mesoporous silica NPs; RANTES, regulated upon activation, normal T cell expressed and secreted; SLNs, solid lipid NPs; Nrf2, nuclear factor erythroid 2-related factor; ANP, atrial natriuretic peptide; COL1A1, collagen type I alpha 1 chain; IL, interleukin; OPN, osteopontin; t-PA, tissue-type plasminogen activator gene; HMGB, high mobility group protein; SMA, smooth muscle actin; CTGF, connective tissue growth factor; Mdivi, mitochondrial division inhibitor; BIO, 6-bromoindirubin-3-oxime; IGF, insulin-like growth factor; TIMP, tissue inhibitor of metalloproteinases; FGF, fibroblast growth factor; FAC, fractional area change; ↑, increased/upregulated; ↓, decreased/downregulated.

a rats model of MI.[102] Margulis and colleagues developed a method to fabricate NPs via a supercritical fluids setup, which loaded and transferred celecoxib, a lipophilic non-steroidal anti-inflammatory drug, into the NPs. These celecoxib-containing NPs alleviated ejection function damage and ventricular dilation by inducing significant levels of neovascularization.[103] Furthermore, a series of investigations indicated that drugs used for hypoglycemia (eg pioglitazone, exenatide and liraglutide)[104–106] and lipid lowering (statins)[107] attenuate the progression of post-MI heart failure, and are therefore also potential therapeutic cargoes for NPs in the treatment of MI.

NP systems also offer an alternative method for delivering plant-derived therapeutic agents, most of which belong to traditional Chinese medicine. It's of vital importance because of the criticization on adverse reactions caused by direct injection of such complexes. Cheng and colleagues designed a dual-shell polymeric NP as a multistage, continuous, targeted vehicle of resveratrol, a reactive oxygen species (ROS) scavenger. Due to the severe oxide stress in areas of infarction, the proposed antioxidant-delivery NPs represent a new method to effectively treat MI. These NPs are modified with two peptides, targeting ischemic myocardium and mitochondria, respectively; cardioprotective effects have been confirmed in both hypoxia/reoxygenated (H/R) H9C2 cells and I/R rats.[108] In addition, Dong and colleagues also demonstrated that puerarin-SLNs produced smaller areas of infarction in a MI rat model, evaluated by 2,3,5-triphenyltetrazolium chloride (TTC) staining. These particles were modified with cyclic arginyl-glycyl-aspartic acid peptide, a specific targeting moiety to αvβ3 integrin receptors, which are highly expressed on endothelial cells (ECs) during angiogenesis.[109] In a recent study, quercetin was loaded into mesoporous silica NPs, which enhanced the inhibition of cell apoptosis and oxidative stress, improving ventricular remodeling and promoting the recovery of cardiac function by activating the janus kinase 2 (JAK2)/STAT3 pathway.[110] Similarly, curcumin–polymer NPs, administered by gavage, improved serum inflammatory cytokine levels compared with direct administration of curcumin.[111]

Translation of novel bioactive agents into clinical practice has been limited, owing to lack of sufficient bioavailability and systemic toxicity.[76] Encapsulating small molecules such as 3i-1000 (an inhibitor of the GATA4–NKX2-5 interaction),[43] TAK-242 (inhibitor of toll-like receptor 4, TLR4)[112] and C143 (inhibitor of ERK1/2)[113]

in NPs promotes myocardial repair after MI without the risk of uncontrolled and off-target adverse effects. Administration of vascular endothelial growth factor (VEGF) causes elevated vascular permeability and tissue edema. The cardioprotective effects of VEGF-loaded polymeric NPs injected either intravenously[114] or intramyocardially[115] eliminated vascular leakage due to promotion of lymphangiogenesis. Further studies have confirmed these results and add to the evidence that combined delivery of VEGF with other growth factors is recommended, since VEGF primarily drives the formation of new capillaries.[116] Furthermore, in line with previous research, similar therapeutic effects have been demonstrated in studies using polymeric NPs loaded with stromal cell derived factor 1 (SDF-1) and insulin-like growth factor 1 (IGF-1).[117,118]

We also notice that some novel payloads in NPs-based therapy for MI have been studied. For example, deoxyribozyme-AuNP can silence tumor necrosis factor-α (TNF-α).[119] A target that is implicated in irreversible heart damage after MI; its effects are mediated by free radical production, downregulation of contractile proteins, and initiation of pro-inflammatory cytokine cascades. Mesoporous iron oxide NPs containing the hydrogen sulfide donor compound diallyl trisulfide act as a platform for the controlled and sustained release of this therapeutic gas molecule. The application of these NPs at appropriate concentrations, resulted in the preservation of cardiac systolic performance without any observable detrimental effects on homeostasis in vivo.[15]

With increasing insight into the molecular mechanisms of MI, a particular emphasis on gene therapy has emerged. Gene expression can be modulated by DNA fragments, messenger RNA (mRNA), microRNA (miRNA) and small interfering RNA (siRNA), which thus represent new approaches for treating ischemia. Currently available nucleic acid delivery systems are mainly divided into viral and non-viral systems. However, virus-based approaches are limited by their potential for uncontrollable mutagenesis.[36] From a clinical point of view, NP represents a suitable choice as novel non-viral nucleic acid vector, which could feasibly transfect in a stable, targeted, and sustained manner (as shown in Table 2).

As a common gene vehicle, plasmids face the risk of being destroyed by DNase and immunoreactivity in the serum, and transduction in non-target organs.[120] A recent study by Kim and colleagues aligns with current research trends focused on virus-free therapies, in which carboxymethylcellulose NPs were designed to transfer 5-azacytidine to halt proliferation, and deliver plasmid DNA containing GATA4, myocyte enhancer factor 2C (MEF2C), and TBX5 to induce reprogramming and cardiogenesis of mature normal human dermal fibroblasts.[121] In a methodological study, lipidoid NPs were used to successfully deliver pseudouridine-modified mRNA, encoding enhanced green fluorescent protein.[122]

MiRNAs act as essential regulators of cellular processes through post-transcriptional suppression; increasing evidence reveals miRNAs play critical roles in cardiovascular diseases. An miRNA-transferring platform with self-accelerating nucleic acid release, containing a heparin core and an ethanolamine-modified poly(glycidyl methacrylate) shell, has been constructed and used as an efficient vector of miR-499, which inhibits cardiomyocyte apoptosis.[123] Intravenous administration of anionic hyaluronan-sulfate NPs (mean diameter 130 nm) enable the stable delivery of miR-21 mimics, thus modulating the expression of TNFα, transforming growth factor (TGF)β, and suppressor of cytokine signaling 1 (SOCS1). Consequently, these NPs switch the phenotype of macrophages from pro-inflammatory to reparative, promote neovascularization and reduced collagen deposition.[124] Interestingly, silencing miR-21 using antagomiR-21a-5p in a nanoparticle formulation has also been shown to reduce expression of pro-inflammatory cytokines in vitro, and attenuate inflammation and fibrosis in mice with autoimmune myocarditis.[125] A number of other potentially therapeutic miRNAs have also been successfully transferred to CMs in recent works, including miR-146a, miR-146b-5p, miR-181b, miR-199-3p, miR-214-3p, miR-194-5p and miR-122-5p.[126–128] Evaluation of angiogenesis, cardiac function, and scar size in these studies indicated that injectable miRNA–NPs can deliver miRNA to restore injured myocardium efficiently and safely. Yang and colleagues developed an in vivo miRNA delivery system incorporating a shear-thinning hydrogel and NPs characterized by surface presence of miRNA and cell-penetrating peptide (CPP).[126] Additionally, angiotensin II type 1 receptor-targeting peptide-modified NPs serve as targeted carriers for anti-miR-1 antisense oligonucleotide, significantly reducing apoptosis and infarct size.[129]

SiRNAs inhibit gene expression by mediating mRNA cleavage in a sequence-specific manner, highlighting NP-based RNA interference as another viable approach to modulate cellular phenotype and attenuate cardiac failure. Dosta and colleagues demonstrated that poly(β-amino ester)

Table 2 NPs-Based Nucleic Acid Delivery Systems for Treatment for MI Reported in the Last 7 Years

Material and Modification Method	Particle Size	Payload	Species and Model	Delivery Method	Therapeutic Effects	Safety in vivo	Ref.
DNA/modRNA delivery system							
Epoxide-derived lipidoid complex (C14-1138)	~155 nm diameter	eGFP modRNA	Rats, LAD; Pigs, embolic coil after balloon occlusion	Intramyocardial injection; ascending aorta (pig only)	eGFP expression↑	No obvious cytotoxicity	[122]
Bioreducible dendrimer polymer		HR1 (a plasmid)	Rats; I/R (LAD for 30min)	Infarct and peri-infarct area injection	LVEF, coronary artery stroke volume, CO, hemodynamic function↑(E); Fibrosis↓		[201]
miRNA delivery system							
Heparin@PGEA	~180nm	miR-499 (alone or with pVEGF)	Mice; LAD	i.v.	LVEF/LVFS/LVIDD/LVIDS improvement; Infarct size, fibrosis and hypertrophy↓; Angiogenesis↑; Apoptosis↓	No evidence of toxicity	[123]
Hyaluronan-sulfate	~130 nm	miR-21 mimic	Mice; LCA	i.v.	LV posterior wall and LV mass; Collagen deposition ↓; Angiogenesis↑; TNFα↓, TGF-β and Socs1↑		[124]
PFBT core with a DSPE-PEG shell, conjugated with CPP	~110nm	miR-199a-3p	Rats; I/R (ligation for 1h)	Peri-infarct area injection; in shear-thinning hydrogel	EF↑; preserved LVESV; Scar size↓; Angiogenesis↑; Proliferation of CMs↑; Expression of HIF1α↑		[125]
Poly(amidoamine)-histidine	60nm	miR-214-3p, miR-194-5p, antagomiR-122-5p	H9c2 and primary cultured CMs		Expression levels of Bax, Bad, Caspase 3 and Caspase 9↓; Apoptosis↓; Cell viability↑		[127]
siRNA/ antisense oligonucleotide delivery system							
Dendrigraft poly-L-lysine, decored with AT1R-targeting peptide, and PEGylated	~200nm	Anti-miR-1 antisense oligonucleotide	Mice; LAD	i.v.	Infarct size↓(Masson-Trichrome)		[130]
PMSNs, combined with PEI	100–200nm	CCR2 siRNA	Mice; LAD	Combined therapy: intramyocardial injection (MSCs) and i.v. (NPs)	Infarct size↓; Angiogenesis↑; Ly6C high monocytes/CD11b-positive monocytes↓	No obvious toxicity	[131]
A polymer–lipid hybrid material, combined with PEG–lipid conjugates	60–80nm	siSdf1, siMcp1	Mice; LCA after 10-week high-fat diet	i.v.	Preserved LV anatomy and function; Infarct size and fibrosis↓; Bone MSCs and leukocytes release↑(siSdf1)/↓(siMcp1); Inflammation of infarction area↓		[202]

(*Continued*)

Table 2 (Continued).

Material and Modification Method	Particle Size	Payload	Species and Model	Delivery Method	Therapeutic Effects	Safety in vivo	Ref.
Lipidoid NPs	50nm	CRMP2 siRNA	ApoE-/- mice; LCA	i.v.	M2 polarization↑; Inflammation, infarct size and fibrosis↓;(Masson's trichrome) Post-MI heart failure and mortality↓		[203]
Lipidoid NPs		IFR5 siRNA	ApoE-/- mice; LCA	i.v.	MMP9/TIMP1↓; healing ↑; HF↓		[204]
Arginine-terminated generation 4 poly(amidoamine) (Arg-G4)	152.2 ±18.5 nm	PHD2 siRNA	Mice; LCA	Intramyocardial injection of Arg-G4-siRNA transfected MSCs	LVEF and LVFS; Infarct area↓; Survival↑		[205]

Abbreviations: eGFP, enhanced green fluorescent protein; PGEA, ethanolamine-modified poly(glycidyl methacrylate); PFBT, poly(9,9-dioctylfluorene-alt-benzothia-diazole); DSPE, 1.2-distearoyl-sn-glycero-3-phosphoethanolamine; CPP, cell-penetrating peptide; PMSNs, photoluminescent mesoporous silicon nanoparticles; PEI, polyethylenimine; MSC, mesenchymal stem cell; AT1R, angiotensin II type 1 receptors; Sdf1, stromal-derived factor 1; CRMP, collapsin response mediator protein; HR1, human Relaxin-expressing plasmid DNA with hypoxia response element 12 copies; IRF5, interferon regulatory factor 5; CO, cardiac output.

particles modified by adding lysine-/histidine-oligopeptides could represent a system for the transfer of siRNA.[130] Studies have now revealed that chemokine C–C motif ligand 2 (CCL2) and its cognate receptor C–C chemokine receptor 2 (CCR2) promoted excessive Ly6C^{high} inflammatory monocyte infiltration in infarcted area and aggravate myocardial injury.[131] Photoluminescent mesoporous silicon nanoparticles (MSNPs) carrying siCCR2 have been reported to improve the effectiveness of transplanted mesenchymal stem cells (MSCs) in reducing myocardial remodeling after acute MI.[131] Targeted transportation and enhanced uptake with minimum leakage improved the efficiency of delivery via NPs, significantly outperforming the control group. Taken together, these studies demonstrate that NPs act as promising drug delivery systems in the treatment of MI.

Enhancement of Cardiac Engineering Biomaterials by Nanoparticles

Myocardial patches and scaffolds, consisting of either bioactive hydrogels or nanofibers, are minimally invasive, relatively localized, and targeted approaches to repair the heart after IHD. Those biomaterials must have an anisotropic structure, mechanical elasticity, electrical conductivity, and the ability to promote ischemic heart repair.[132] A variety of NPs have been applied in this field, among which inorganic NPs have been the focus of most research efforts.[42] These investigations of inorganic NPs can be divided into four categories based on their effects and the mechanisms involved, which are described in this section.

NPs enhance physical properties and electroconductivity, which is essential for the biomaterials to properly accommodate cardiac cells and subsequently resulted in cell retention, cell-cell coupling and robust synchronized beating behavior. CNTs are able to increase the required physical properties of scaffolds, such as maximum load, elastic modulus, and toughness.[133,134] Gelatin methacrylate (GelMA) also has decreased impedance, hydrogel swelling ratio, and pore diameter, as well as increased Young's modulus when combined with gold nanorods (AuNRs).[135] Given this insight, highly electroconductive NPs have been increasingly investigated.[34,99] Specifically, Ahadian and colleagues revealed that a higher integrated CNT concentration in gels resulted in greater conductivity.[136] Zhou and colleagues verified the therapeutic effects of patches incorporating single-walled CNT for myocardial ischemia, which halted progressive cardiac dysfunction and regenerated the infarcted myocardium.[137] Spherical AuNPs have also been shown to increase the conductivity of chitosan hydrogels in a concentration-dependent manner.[138] Interestingly, silicon NPs mimic the effects of AuNRs without affecting conductivity or stiffness, as reported by Navaei and colleagues.[139]

Several studies demonstrate the effects of CNT on CM functions. When CMs are cultured on multi-walled CNT substrates or treated with CNT-integrated patches, these cells show spontaneous electrical activity.[34,99,140] Brisa and colleagues functionalized reverse thermal gels with AuNPs, investigating the phenotype of CMs in vitro; the growth of cells with a CM phenotype was observed, along with gap junction formation.[141] CMs exposed to AuNR-containing GelMa show higher affinity, leading to packed and uniform tissue structure.[135] These conductive scaffolds also facilitate the robustness and synchrony of spontaneous beating in CMs without damaging their viability and metabolic activity.

Combined incorporation of inorganic NPs and cells represents a feasible strategy to promote therapeutic effects. Despite some reports on the cytotoxicity of Au,[89,90] no significant loss of viability, metabolism, migration, or proliferation of MSCs in scaffolds containing AuNP is reported. A CNT-embedded, electrospun chitosan/polyvinyl alcohol mesh is reported to promote the differentiation of MSCs to CMs.[142] In another approach, Baei and colleagues added AuNPs to chitosan thermosensitive hydrogels seeded with MSCs.[138] There was a significant increase in expression of early and mature cardiac markers, indicating enhanced cardiomyogenic differentiation of MSCs compared to the matrix alone, while no difference in growth was observed. Gao et al created a fibrin scaffold, in which cells and AuNPs were suspended simultaneously; these bioactive patches were shown to promote left ventricular function and decrease infarct size and apoptosis in the periscar boarder zone myocardium in swine models of acute MI.[97] These studies of AuNP-containing scaffolds demonstrated reduced infarct and fibrotic size, as well as facilitated angiogenesis and cardiac function, which can be attributed at least in part to the enhanced expression of connexin 43 and atrial natriuretic peptide, and activation of the integrin-linked kinase(ILK)/serine-threonine kinase (p-AKT)/GATA4 pathway.[49,143,144] Scaffolds containing Ag NPs evoke M2 polarization of macrophages in vitro;[145] which may also play a role in cardioprotective action because M2 macrophages are capable of promoting cardiac recovery via the secretion of anti-inflammatory cytokines, collagen deposition, and neovascularization.[146]

Similarly, CNT also act synergically with poly (N-isopropylacrylamide) scaffolds containing adipose-derived stem cells;[147] significant improvement of cardiac function and increased implantation and proliferation of stem cells has been observed with these scaffolds, compared with scaffolds without CNT.[147] Selenium NPs[148] and titania NPs[53] have been shown to improve the mechanical and conductive properties of chitosan patches, promoting their ability to support proliferation and the synchronous activity of cells growing on these patches.

Mounting evidence demonstrates the unique benefits of using cardiac scaffolds with magnetic NPs such as SPIONs; these benefits include, but are not limited to, significant improvements in cell proliferation[149] and assembly of electrochemical junctions.[150] Given that magnetic manipulation enhances the therapeutic efficacy of iron oxide NPs in cardiac scaffolds, Chouhan and colleagues designed a magnetic actuator device by incorporating magnetic iron oxide NPs (MIONs) in silk nanofibers; this resulted in more controlled drug release properties, as well as the promotion of proliferation and maturation in CMs.[151] Magnetic NPs can be used to label induced pluripotent stem cell (iPSC)-derived CMs via conjugation with antibodies against signal-regulatory protein α. Zwi-Dantsis and colleagues reported the construction of tailored cardiac tissue microstructures, achieved by orienting MION-labelled cells along the applied field to impart different shapes without any mechanical support.[152] However, the interactions between and effects of NPs and cells in scaffolds, and the cardioprotective efficacy of patches in which NP-labelled cells are suspended, require further elucidation.

Polymeric nanomaterials have also been investigated in the context of cardiac bioengineering materials; for instance, water-swollen polymer NPs have been used to prepare nanogels. With a 3D structure containing cross-linked biopolymer networks, nanogels can encapsulate, protect, and deliver various agents.[83,153] PDA-coated tanshinone IIA NPs suspended in a ROS-sensitive, injectable hydrogel via PDA-thiol bonds significantly improved cardiac performance, accompanied by inhibition of the expression of inflammation factors in rat model.[73] After implanting cryogel patches consisting of GelMa and linked conductive polypyrrole NPs[154] or scaffolds of electrospun GelMA/polycaprolactone with GelMA-polypyrrole NPs,[155] left ventricular (LV) ejection fraction (EF) has been shown to increase, with a concurrent decrease in infarct size, in MI animal models.

Combined Nanoparticle–Cell Strategies

Progenitor or stem cell-based therapy in the form of injections and engineered cardiac patches, discussed in the

previous section, has been recognized as a promising strategy to improve the cardiac niche and ameliorate adverse remodeling processes and fibrosis after acute MI.[56,156,157] However, poor survival and low engraftment rates for transplanted cells are still major challenges in this field.[157] Among possible optimization strategies, combining NPs with stem cell therapy is of great interest (Table 3).

Accumulating evidence has shown two main mechanisms for NP-loaded cell therapy in the context of MI treatment. Firstly, various NP types could efficiently improve survival and cell proliferation, modulating differentiation of implanted cells in the ischemic microenvironment.[62,158] Specifically, electrically driven nanomanipulators could guide cardiomyogenic differentiation of MSCs: in a previous study, electroactuated gold NPs were administrated with pulsed electric field stimulation, and tube-like morphological alterations were observed, along with upregulation of cardiac specific markers.[143] Adipose-derived stem cells that load PLGA-simvastatin NPs promoted differentiation of these cells into SMCs and ECs, and had cardioprotective effects in a mouse model of MI induced by left anterior descending ligation.[17] Secondly, engraftment rate is another important factor affecting treatment efficacy in this context.[159] Zhang and colleagues designed silica-coated, MION-labelled endothelial progenitor cells; intravenous administration of these cells in a rat model of MI significantly improved cardiac performance, as indicated by echocardiogram, morphological, and histological evidence, and neovascularization. This indicates magnetic guidance may potentially address the problem of low levels of stem cell retention, which has typically been observed.[51] In particular, NPs can link the therapeutic cells to injured CMs, thereby promoting cell anchorage and engraftment. To this end, Cheng and colleagues established a magnetic, bifunctional cell connector by conjugating NPs with two antibodies: one against cell determinant (CD)45, which is expressed on bone marrow-derived stem cells, and one against MLC. The magnetic core of this NP also enabled physical enrichment in ischemic heart tissue using external magnets.[160] More than one mechanism may be involved in a study. Chen and colleagues fabricated a sustained release carrier of insulin-like growth factor (IGF), a pro-survival agent, via in situ growth of Fe_3O_4 NPs on MSNPs. In this study, the NPs promoted both the survival and retention of MSCs, and intramyocardial injection of the NP-labeled MSCs was able to ameliorate functional and histological damage without any obvious toxicity in vivo.[161] However, SPION labeling does not seem to improve therapeutic efficiency, as demonstrated by Wang and colleagues in a study using hypoxia-preconditioned SPION-labeled adipose-derived stem cells (ASCs).[162]

Application of Exosomes in MI Treatment

Primary criticisms of cell-based therapies include their potential immunogenicity, arrhythmogenicity and tumorigenicity. It is widely accepted that the beneficial effects of cell-based therapy are mainly attributable to paracrine effects rather than directly replenishing lost CMs;[56] researchers are therefore investigating of cell-free approaches. Exosomes have attractive properties including stable transport, homing to target tissues or cells, and penetration of biological barriers, as well as being more biocompatible with lower immunogenicity than cell-based approaches. Interestingly, post-MI circulating exosomes serve as important cardioprotective messengers.[163,164] Manipulating their biodistribution has proven to be a viable strategy to reduce infarct size, promoting angiogenesis and ejection functions.[21] However, from a therapeutic standpoint, the lack of control over endogenous exosome production and cargo encapsulation limits the use of this naturally-present mechanism for therapeutic enhancement. The low purity and weak targeting of natural exosomes are two further obstacles to overcome before clinical application. Strategies to address these include finding robust sources; optimized isolation methods for higher yields, efficiency and purity; and improving therapeutic payloads. These have been systematically summarized in other reviews.[165–167]

Nanoparticle-Based Prevention Strategies for Myocardial Infarction

AS is considered a low-grade, chronic inflammatory disease, characterized by accumulation and deposition of cholesterol in arteries, as well as remodeling of the extracellular matrix in the intima and inner media.[12,168] Inflammation of ECs, proliferation of SMCs, and recruitment of monocytes and macrophages play a critical role in the development of AS. NPs allow for the packaging of large amounts of therapeutic compounds in a compact nanostructure, specifically targeting pathological mechanisms and attenuating atherogenesis. Optimization of the loaded drug and NP target together lead to enhanced efficacy while minimizing side effects.[169] In this section, we summarize recent breakthroughs in the order of pathological progression, as shown in Table 4.

Table 3 Studies Combining NPs and Cell Therapy Reported in the Last 7 Years

Material of NPs	Modification and Drug Loading	Cell Type	Species and Model	Delivery Method	Cardiac Therapeutic Effects and Assessment Method				Safety	Ref.
					Function and Hemodynamy	Necrosis and Fibrosis	Angiogenesis	Other Effects		
NP-ASCs combined system										
PLGA	Loading of simvastatin	ASCs	Mice; LAD	i.v.	LVEF, LVIDD/LVISD↑(E)	LV fibrosis length, infarct size↓; scar area wall thickness↑; cardiac granulation tissue development and regeneration (Masson's trichrome, IF)	↑(IHC)	Differentiation into SMCs and ECs↑; VEGF, IGF-1↑; apoptosis(TUNEL)↓		[17]
SPION		ASCs	Rats; LAD	Intramyocardial injection (with external magnetic field)	LVEF↑; LVEDV, LVESV↓(MRI)		↑(IF or IHC)	Levels of HIF-1α, VEGF, HGF, IGF-1↑; CMs apoptosis↓		[18, 162]
Fullerenol NPs		ASCs	Rats; LAD	Infarction border zone injection (in alginate hydrogel)	LVIDS↓LVIDD↓LVEF↑LVFS↑	MI size↓(Masson's trichrome)		ROS↓(cell study)		[206]
Lipid-based NP emulsion	Loading of cyclosporine A	ASCs	Swine; I/R by LAD	Intracoronary injection	LVESV↓(MRI)	MI size↓(IF)	↑(IF)	ASCs survival↑(IF)		[207]
PLGA	Modification with mPEG; loading of melatonin	ASCs	Rats; I/R by LAD	Infarction border zone injection	LVEF↑			ASCs survival↑(bioluminescence imaging)		[208]
Au	Functionalization with amine compound	MSCs	Mice; cryoinjury	Extracellular matrix/ silk protein fibroin patches	Wall thickness↑(HE staining)	Infarct size and fibrosis↓(HE staining)		Retention and cell activity of MSCs on patches↑		[44]
NP-MSCs combined system										
IONP		MSCs	Rats; I/R by LAD	Infarction border zone injection		MI size↓ Fibrotic tissue formation↓(Masson's trichrome)	↑(IF)	Connexin 43↑(IF); Survival↑(TUNEL)		[164]

(*Continued*)

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Table 3 (Continued).

Material of NPs	Modification and Drug Loading	Cell Type	Species and Model	Delivery Method	Cardiac Therapeutic Effects and Assessment Method				Safety	Ref.
					Function and Hemodynamy	Necrosis and Fibrosis	Angiogenesis	Other Effects		
MagBICE2 (Feraheme NPs)	Conjugating with anti-CD45 and anti-MLC antibodies	Bone marrow-derived MSCs	Rats; I/R by LAD	i.v.		MI size↓(Masson's trichrome)		Binding in heart↑(IF)		[160]
Silica-IONP	Loading of IGF	MSCs	Mice; I/R by LAD	Intramyocardial injection	LVEF and global longitudinal strain↑(E)	Cardiomegaly and fibrosis↓(HE, trichrome staining)		Survival and retention of MSCs↑; MCP1, VEGF, HGF↑; TGFβ↓	No toxicity in vivo	[161]
System of NP combined with other cell types										
Silica-coated MIONs		EPCs	Rats; LAD	i.v. (followed by external magnetic field for 1h)	LV wall thickness↑, ventricular dilatation↓ (Masson's trichrome)	Fibrosis markers↓; fibrosis area and infarct size↓ (Masson's trichrome)	↑(IF)	Retention of EPCs↑; apoptosis↓(TUNEL)		[51]
Ferumoxytol NPs		CDCs	Rats; I/R by LAD	Coronary injection (with magnetic field for 10 min)	EF↑(E)		↑(counting)	Cell retention↑		[159]
Magnetic NP-containing liposomes		Multilayered ADRCs sheets	Mice; I/R by LAD	Injection in the ischemic heart	LVFS, LVEF↑(E)	Interstitial fibrosis↓(Masson's trichrome)	↑ (IF)			[209]

Abbreviations: ASCs, Adipose-derived stem cells; IONP, iron oxide NPs; MIONs, magnetic IONP; SPION, superparamagnetic IONP; HGF, hepatocyte growth factor; EPCs, endothelial progenitor cells; CDCs, cardiosphere-derived stem cells; MagBICE, magnetic bifunctional cell engager; ADRCs, adipose-derived regenerative cells.

Table 4 NPs-Based Preventive Strategies for MI Reported in the Last 7 Years

Materials and Modifications	Particle Size	Payload	Species and Model	Therapeutic and Preventive Effects	Safety	Ref.
Primary prevention						
PLA	~279nm (by SEM)	Aliskiren	Spontaneously hypertensive rats	BP↓; vasoactivity of mesenteric artery Collagen content in the aorta↓; Fibrosis of aortic tunica media↑ LV total NOS and neuronal NOS↑; endothelial NOS↓		[29]
Biscarbamate-crosslinked Gal-PEG -PEI NPs		AGT shRNA	Spontaneously hypertensive rats	BP↓; Heart hypertrophy↓; Myocardial ultrastructure improvement		[172]
PLGA		Propylene glycol alginate sodium sulfate	Rats; 8-week streptozotocin induced diabetic cardiomyopathy	LVEF, FS↑; LVISD, LVIDD↓ Myocardial morphology↑ Coronary microcirculation↑ Plasminogen activator inhibitor-1 expression in CMs↓; TNF-α, IL-1β, IL-6↓; NF-κb and AGEs/RAGE pathway↓; serum SOD and GSH↑		[210]
Hyaluronic Acid		Curcumin	Hypertensive, heterozygous rats	BP↓		[211]
Lipid NPs	65~75nm	ApoB siRNA	Lean rhesus macaque	LP(a) ↓		[212]
SLNs	180–220 nm	Candesartan cilexetil	Rats; oral fructose solution	BP↓; bioavailability↑		[213]
Avoiding AS development						
Lipid mixture	60nm	Docetaxel	Rabbits; 8-week high-cholesterol diet	Atheroma area↓; levels of caspase 3, caspase 9, Bax, Bcl-2, MMP-2, MMP-9, TGF-β, NF-κB, TNF-α, IL-1β, IL-6, PCNA, vWF, collagen 1 and 3 in the aortic arch↓	No obvious toxicity	[9]
Leukosomes (liposome); Fabricated with membrane proteins of macrophages	108±2.3 nm	Rapamycin	Mice; 12-week high-fat diet	Plaque burden↓; proliferating macrophages in the aorta↓; MCP-1, IL-b1, MMP↓	Good tolerance	[90]
PEGylated SWNTs	5–6 nm	SHP1i	ApoE-/- mice; subcutaneous angiotensin II–infusing minipumps or 11-week high-fat diet	Plaque burden↓; lesional phagocytosis↑; inflammatory genes in lesional macrophages↓	Favorable safety profile	[177]
rHDL		TRAF-STOPs	ApoE-/- mice	Atherosclerotic plaques↓; leukocyte recruitment↓; Macrophages activation↓	No hepatotoxicity or functional hyposplenism	[178]

(*Continued*)

Table 4 (Continued).

Materials and Modifications	Particle Size	Payload	Species and Model	Therapeutic and Preventive Effects	Safety	Ref.
PEI	~45nm	ICAM1, ICAM2, VCAM1, Sel-E, Sel-P siRNAs	ApoE-/- mice; high-cholesterol diet and I/R injury (LAD for 45min)	Neutrophil and monocyte recruitment↓, matrix-degrading plaque protease activity↓		[187]
PLGA	214.3±0.6nm (SRM-NP); 216.9±0.6nm (PTX-NP)	Sirolimus (SRM-NP) or paclitaxel (PTX-NP)	Mini-pigs; temporary carotid closure and balloon angioplasty	Vascular stenosis and expression of PCNA↓, glycolysis and expression of HIF-1α in hypoxic ECs and SMCs↓		[214]
Lipid mixture	53.9–95.9nm	Curcumin	Rats; temporary carotid closure and balloon angioplasty	Neointimal formation↓;		[215]
PLGA (SPN) or liposome (LIP)	208±2nm (SPN); 174 ±2nm (LIP)	Methotrexate	Mice; 28-day high-fat diet	Intracellular lipids and oxidized LDL↓; RANTES, IL-1β, TNFα↓; IL-1α↑		[216]
PEG and sebacic acid	~100nm	D-PDMP	Mice; 8-week high-fat and cholesterol diet	AS plaque buildup, cholesterol ester crystal deposits, and fibrosis↓; FS↑ and cardiac hypertrophy↓ Oxidized LDL↓; changes of levels of genes associated with triglyceride metabolism		[217]
Lipid NPs	45 to 60 nm (Ref. 219)	Methotrexate or paclitaxel	Rabbits; high-cholesterol diet (with heterotopic heart transplantation and CsA administration in Ref. 218)	Coronary stenosis, macrophages infiltration↓; gene expression of TNFα, MCP1, IL-18, VCAM1, and MMP12↓; expression of IL-10 ↑; Macroscopic atheroma plaque area↓		[218,219]
Lipid NPs	60 nm	Carmustine	Rabbits; 8-week cholesterol diet	Lesion areas↓ Macrophages, FOXP3, IL-1β, LDL-R↓		[220]
Avoiding plaque rupture and thrombosis						
PEG/PEI (Loaded into an E-selectin-targeting multistage microparticles)		miR-146a, miR-181b	ApoE-/- mice; 12-week western diet	Plaque size↓; Stabilization↑		[126]
Perfluorocarbon and excipient combined with alpha(nu)beta(3)-integrin antagonist		Fumagillin	Hyperlipidemic rabbits; 100-day cholesterol diet	Acute antiangiogenic effects		[182]

(*Continued*)

Table 4 (Continued).

Materials and Modifications	Particle Size	Payload	Species and Model	Therapeutic and Preventive Effects	Safety	Ref.
Albumin (linked to microbubbles)	~225.6nm	t-PA plasmid	Dogs; coronary bypass using the autoallergic saphenous vein	Thrombotic rate↓; Intimal thickness and proliferation of SMCs↓; t-PA and D-dimer contents in blood↑		[183]
Amphipathic, cationic peptide	~55nm	JNK siRNA	Mice; 14-week western diet	Barrier permeability and disruption↓; Foam cell formation, plaque necrotic area and Macrophages↓; Thrombotic risk↓; NF-κB and STAT3 expression↓	No toxicity in vivo	[184]
PEGylated and cRGD-coated liposomes	164.6±5.3 nm	t-PA	In vitro	Affinity↑; Fibrin clot lysis↑		[221]

Abbreviations: SEM, scanning electron microscope; NOS, nitric oxide synthase activity; AGT, angiotensinogen; GSH, glutathione; LP(A), lipoprotein(A); PCNA, proliferating cell nuclear antigen; vWF, von Willebrand factor; SWNTs, single-walled carbon nanotubes; SHP1i, SH2 domain-containing phosphatase-1 inhibitor; rHDL, recombinant high-density lipoprotein; TRAF-STOPs, tumor necrosis factor receptor associated factor (TRAF) 6; ICAM, intercellular cell adhesion molecule; VCAM, vascular cellular adhesion molecule; Sel, selectin; D-PDMP, D-Threo-1-phenyl-2-decanoylamino-3-morpholino-1-propanol; LDE, lipid nanoparticle; cRGD, cyclic arginine-glycine-aspartic acid.

Primary prevention refers to control of the risk factors of AS, one of which is hypertension.[170] PLA NPs have been shown to improve the efficacy of aliskiren, the first oral direct renin inhibitor and the first in a new class of antihypertensive agents.[29] Encapsulation in nanocarriers also renders the application of anandamide viable, which was once limited; recent research revealed that this new therapy could lower blood pressure and LV mass index in rats.[171] Similar results were observed in a study in which angiotensinogen was silenced using small hairpin RNA.[172] NPs may also help to make more anti-hypertensive drugs available, reduce side effects such as asthma, and lessen the effective dosage by providing sustained drug release over time. The link between AS and diabetes mellitus, which describes a group of metabolic disorders, has also been investigated in numerous studies.[173] Possible mechanisms include oxidative stress, altered protein kinase signaling, and epigenetic modifications. Cetin and colleagues successfully constructed NP-based drug delivery systems for the administration of metformin, an oral antihyperglycemic agent with low oral bioavailability and short biological half-life.[174] NPs are also promising tools for improving the oral bioavailability of insulin, which is of great interest because oral insulin will significantly increase patients' compliance.[175,176]

The inflammatory hypothesis of AS is now widely established, making selective targeting and accumulation of NPs in inflammatory lesions attractive therapeutic strategies. Targeting macrophages in apoE-/- mice has been shown to result in decreased phagocytosis and suppression of inflammatory genes in lesional macrophages, thus lessening burden of atherosclerotic plaques.[177] Tom and colleagues used NPs consisting of high-density lipoprotein (HDL), a known atheroprotective bionanomaterial, as carriers for TNF receptor-associated factor in mice, and observed reductions in both leukocyte recruitment and macrophage activation.[178] Both single-walled CNT and HDL-NPs have a favorable safety profile. In a pathological context, activated endothelial tissue expresses more adhesion molecules, such as selectins, than usual. These molecules are thus potential targets for cardiovascular nanomedicine. Glycoprotein Ib (GPIb)[179] and biotinylated Sialyl Lewis A (sLeA)[69] specifically bind to selectins, leading to the accumulation of conjugated NPs in injured vessels; an in vitro study demonstrated that GPIb-conjugated NPs could bind to target surfaces, where they were taken up by activated ECs under shear stress conditions. In another study, Sager and colleagues simultaneously inhibited five adhesion molecules associated with leukocyte recruitment in post-MI apoE-/- mice. Inflammation in plaque and ischemic heart, rendering acute coronary events and post-MI complications less likely to occur.[180] However, targeting inflammatory process may have heterogeneous effects in humans

because the targeting moieties and target receptors may be overexpressed in several different pathologic conditions in addition to AS. Oxidation is another factor involved in the development of AS. Upregulation of endothelial nitric oxide synthase (eNOS) leads to vascular construction and other AS-promoting effects. Pechanova and colleagues observed that the application of PLA NPs resulted in larger decreases in NOS than direct administration.[29]

Aside from these processes, avoiding plaque rupture and thrombosis could be another therapeutic aim. Nakashiro and colleagues showed that delivering pioglitazone via NPs inhibited plaque rupture in apoE-/- mice.[181] The integrin αvβ3 is upregulated in angiogenic vasculature, which is ubiquitous in plaque ruptures, which may lead to MI.[182] αvβ3 integrin-targeted NPs provide a site-specific drug delivery platform that has been shown to successfully stabilize plaques in rabbits.[182] Ji and colleagues used NPs composed of albumin with an average diameter of 225.6 nm to deliver a plasmid containing the tissue-type plasminogen activator gene (t-PA); this system plays a role in preventing thrombosis in addition to attenuating intimal thickness and proliferation of vascular SMCs.[183] NPs consisting of engineered amphipathic cationic peptide and serine/threonine protein kinase JNK2 siRNA also reduces thrombotic risk, plaque necrotic area, and vascular barrier disorder in mice given the equivalent of a 14-week western diet.[184]

The Future Prospects

Innovation and development of therapies based on NPs in recent years has led to significant advances towards complete repair of the injured myocardium following acute MI. Nevertheless, developing clinically relevant solutions remains difficult for several reasons. Firstly, as shown in tables, there is little consistency among studies regarding the characteristics of NPs, their payloads, and their methods of administration, as well as methods used for evaluating cardiac repair. It can be difficult to control characteristics such as the size of the synthesized particles in a narrow range, even within single studies. Such significant heterogeneity can lead to differences in observed results in repeated experiments, or under different conditions. Secondly, although many studies have focused on the health effects of unintentional exposure to NPs by inhalation or ingestion,[185,186] most of the studies on medical applications of NPs have not reported on toxicity of NP systems until recently.[73] Remarkably, there has not been a consensus on NP-associated adverse effects in existing reports, making assessments of biocompatibility a priority for NP characterization.

NPs have emerged as a powerful tool for controlling cell signaling pathways in regenerative strategies using novel therapeutics and drugs that are unsuitable for direct administration. One advantage of the application of NP systems is the ability to release the drug payload or regulate gene expression in a stable and controlled manner. Therefore, many otherwise serious side effects, such as sudden arrhythmic deaths resulting from persistent and uncontrolled expression of miRNA by viral vectors, may be completely avoided.[187] More research is required to develop stable and efficient methods of NP production, improve encapsulation efficiency of drugs, and achieve satisfactory targeting. In particular, a greater focus on investigating NP-based switches, including optical, electrical and magnetic methods, has enabled the regulation of cell signaling, exemplified by the development of a CuS NP-based photothermal switch.[52] Optimizing tissue engineering scaffolds containing conductive NPs is a promising strategy for the protection of the myocardium after ischemia by mimicking the myocardial extracellular matrix. Improvements in understanding of cardiac repair mechanisms, and how these biomaterials may interfere with them, is therefore urgently needed. Furthermore, heart repair is complex and involves many processes, including apoptosis, angiogenesis, inflammatory infiltration, and fibrosis. Therefore, novel treatments should be designed using NP-based integrative strategies based on these multiple different mechanisms. However, it's important to highlight that synergistic effects of different drug payloads, NPs, and NP–cell combined strategies should be addressed, as not all may be compatible with one another. Future research should focus on these aspects to translate NP-based therapeutic strategies for MI into practical and effective clinical use.

Disclosure

The authors report no conflicts of interest in this work.

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