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Developing injectable nanomaterials to repair the heart Current Opinion in Biotechnology, (34) Nanobiotechnology 2015

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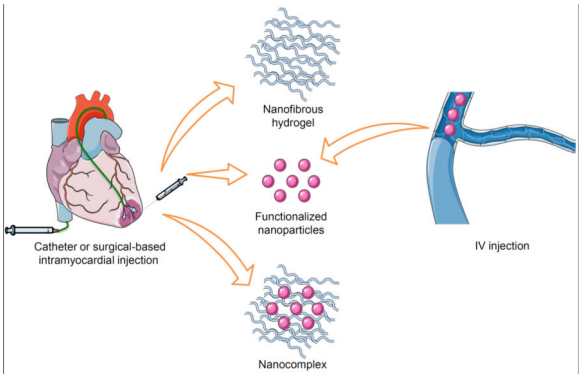
Abstract

Injectable nanomaterials have been designed for the treatment of myocardial infarction, particularly during the acute stages of inflammation and injury. Among these strategies, injectable nanofibrous hydrogel networks or nanoparticle complexes may be delivered alone or with a therapeutic to improve heart function. Intramyocardial delivery of these approaches localizes treatments to the site of injury. In an alternative approach, nanoparticles may be delivered intravenously, which provides the ultimate minimally invasive approach. These systems take advantage of the leaky vasculature after myocardial infarction, and may be designed to specifically target the injured region. The translational applicability of both intramyocardial and intravenous applications may provide safe and effective solutions upon optimizing the timing of the treatments and biodistribution.

Graphical abstract



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Introduction

Myocardial infarction (MI) accounts for 1 in 6 of the total deaths in the U.S. [1]. Immediately after MI, the myocardium is unstable because of cell death and the physical and biological changes to the damaged extracellular matrix (ECM). As the ECM degrades, the left ventricle (LV) wall is weakened, thinning overtime [2]. Early healing processes involve the inflammatory response, causing the migration of neutrophils and macrophages to the injured site [3,4]. The ECM continues to degrade for over a week, and within three weeks, myofibroblasts invade the infarct area and a collagen scar begins to form. Late LV remodeling may continue for months to years, and may eventually lead to chronic heart failure [5]. Early intervention has the potential to minimize the adverse effects during the initial inflammatory stage and preserve borderzone cardiomyocytes, which are at risk of ongoing apoptosis, thereby slowing or inhibiting the progression of negative LV remodeling. In this review, we will focus on injectable nanomaterials recently under investigation for treating MI (Table 1).

Injectable biomaterials designed to treat MI during the early stages of remodeling are frequently administered through intramyocardial, intracoronary, or intravenous (IV) routes (Figure 1). Intramyocardial injections have the advantage of localized therapy while minimizing potential systemic effects [5]. Intramyocardial injections may be accomplished by either catheter delivery or directly administered through a surgical approach with a syringe and needle. The former is a minimally invasive approach requiring only sedation, while the latter is an invasive surgery requiring general anesthesia [6]. When incorporated with a therapeutic, the bioactivity of the molecule should be maintained, released, and delivered in a sustained manner. Local intramyocardial delivery to the injured myocardium has been shown to reduce collagen scar formation and improve heart function. However, injecting a biomaterial during the acute time window is unlikely to be clinically acceptable, due to an increased risk of ventricular rupture [6–8]. The safety of intramyocardial injections in the very acute MI stages remains a clinical concern and should continue to be critically evaluated.

Intracoronary and IV delivery of biomaterials take advantage of the enhanced permeability and retention (EPR)-like effect that occurs after myocardial injury [9,10]. The leaky vasculature allows the transport of materials to enter the infarcted zone. *In vivo* studies investigating catheter-based intracoronary infusion of nanoscale biomaterials has not been demonstrated; however, interesting work has been published on alginate-derived hydrogels using this delivery method [11,12]. IV injection of biomaterials is the ultimate minimally invasive approach that delivers treatments directly into the blood stream with the goal of accumulating in the MI. Nanoparticles designed for IV delivery should not aggregate during injection or transport, leach functionalized therapies while in the bloodstream, nor cause systemic toxicity. IV treatments minimize potential procedure costs and time, but the biodistribution and clearance of the injected materials remains an important issue and is influenced by the size, shape, and charge of the molecule [13,14].

Intramyocardial delivery of nanoscale biomaterials: nanofibrous hydrogels and nanoparticle systems

Treatments developed to reduce LV remodeling include injectable hydrogels, which have shown promise in preventing heart failure [6,15,16]. Injectable hydrogels should form a gel in the injured area, and be biocompatible and biodegradable. While injectable hydrogels have been postulated to affect cardiac function via increasing wall thickness and reducing wall stress via La Place's Law [15], recent studies have shown that passive wall thickening does not increase function, but rather the bioactive or cell response to these materials influences positive remodeling outcomes and increases in cardiac function [17,18]. Hydrogels that are designed to have nanoscale fiber networks, mimic the native ECM, and thereby create a new scaffold to facilitate cell recruitment. Some nanofibrous hydrogel scaffolds have shown promise *in vitro*, but their delivery in an infarcted animal model remains uninvestigated [19,20]. Other hydrogel networks have been investigated as nanofibrous scaffolds to treat MI, but these invasive approaches have sutured the biomaterial directly to the heart [21,22]. Ideally an injectable hydrogel should be delivered via catheter to obviate the need for invasive surgery and general anesthesia. In this case, the hydrogel must also have the appropriate resistance and gelation kinetics to facilitate multiple injections required of a transendocardial delivery approach, and be hemocompatible and not result in embolism since some leakage into the blood stream is known to occur [6].

Injectable, self-assembling peptides are one class of nanofibrous hydrogels that have been examined for treating MI. These are composed of relatively short peptide sequences that assemble into a nanofibrous, hydrogel network under physiological conditions, as shown with RAD16-II, which forms fibers on the order of 5 nm in diameter [23–25]. The delivery of vascular endothelial growth factor (VEGF) has been explored using RAD16-II as a carrier in both rodent and porcine models [26]. VEGF was released from the nanofibrous hydrogel network at a steady rate over 14 days. Improved heart function and neovascularization was observed in the group treated with both VEGF and RAD16-II, compared to the saline and material only controls in both animal models. The self-assembling peptide RAD16-II has also been modified to contain a heparin-binding motif to sequester and deliver VEGF in a rodent MI model [27]. The newly designed material did not affect self-assembly properties and formed nanofibers roughly 10 nm in diameter. Improved heart function, decreased infarct size, and increased angiogenesis were observed in groups that received VEGF with either RAD16-II or modified with heparin, although all measures trended higher in the later combination.

Injectable hydrogels derived from decellularized ECM are another class of nanofibrous hydrogels that have been examined for treating MI [28–31]. To make an injectable hydrogel, the decellularized ECM is partially digested, creating a liquid material that self-assembles into a nanofibrous network upon injection with fiber diameters of approximately 40–100 nm [28]. A cardiac specific ECM hydrogel, derived from porcine ventricular myocardium, has been shown to be biocompatible, recruit cardiac progenitors, stimulate neovascularization, increase cardiac muscle, and reduce infarct fibrosis in small and large animal MI models [29,31]. The hydrogel, which is compatible with percutaneous transendocardial delivery, degrades upon cell infiltration within 2–3 weeks *in vivo*, yet significant increases in cardiac

function were observed 3 months post-injection when delivered 2 weeks post-MI [31]. When processed appropriately, ECM derived hydrogels retain native sulfated glycosaminoglycans (sGAGs) [28,30], which can retain and enhance activity of delivered growth factors. This has been shown with a pericardial ECM hydrogel, where retention and increased activity of basic fibroblast growth factor (bFGF) and an engineered hepatocyte growth factor (HGF) were observed in rat MI models [30,32].

Several other nanoscale materials have also been explored as injectable delivery vehicles for treating for MI. In designing these systems, the molecule should be released at a controlled rate, from either nanofiber or nanoparticle carriers, while providing therapeutic effects *in vivo*. For example, a synthetic polymer composed of ureido-pyrimidinone and polyethylene glycol (PEG) was used to deliver hepatocyte growth factor (HGF) and insulin-like growth factor (IGF-1) via catheter injection [33]. Both IGF-1 and HGF were released from the hydrogel by 4 days *in vitro*. The initial burst release of IGF was lower than for HGF, most likely due to the size of the proteins. In another study, a hybrid nanosystem composed of a methacrylated gelatin hydrogel and polyethylenimine functionalized graphene oxide nanosheets was developed for gene delivery of VEGF-165 [34]. The researchers demonstrated slow release of VEGF-165 over 3 days *in vitro*. When injected 15 minutes post-ligation, treated groups did not show signs of toxicity or inflammation 7 days post-injection. Improved cardiac function, measured by ejection fraction, and angiogenesis was also observed in treated groups compared to the control groups 14 days post-injection.

Systemic treatment with nanoparticles through passive delivery

Nanoparticles are attractive for minimally invasive delivery because they may be administered with IV injection and target the heart through the EPR effect that is present in the acute stages of MI. Similar to trends observed for intramyocardial injections, the size of the nanoparticle may affect accumulation and distribution with IV injections. For example, gadolinium-containing micelles and liposomes, 15 and 100 nm in diameter, respectively, were injected IV into infarcted mice 24 hours post-injury [37]. Both the micelles and liposomes demonstrated longer circulation times than gadolinium alone. The micelles accumulated more quickly than the liposomes, and both materials remained in the infarct 24 hours post-injection. Two days after injection, the micelles were only observed in the kidneys, while the liposomes were present in the spleen and liver. When injected 7 days post-MI, both sets of particles accumulated in the infarct and were cleared within an hour. These results suggest that both particle size and timing of injection after injury play important roles in accumulation and circulation.

An advantage of IV delivery is the ability to deliver at very early time points post-MI, which has the potential to mitigate detrimental negative LV remodeling. For example, VEGF-encapsulated liposomes were designed as an approach to safely deliver VEGF [38]. When the liposomes were injected IV immediately after ligation, significant improvements in heart function and vascular density were observed 4 weeks after injection compared to groups that received liposomes alone or free VEGF. Another example of immediate delivery has been shown with dodecafluoropentane nanoparticles to deliver oxygen [39]. The therapy was

injected IV immediately after ligation, and a 60% decrease in infarct size was observed compared to those treated with saline.

Systemic treatment with nanoparticles through targeted delivery

In addition to taking advantage of passive targeting with the EPR effect, nanoparticles can also be designed to bind to specific targets that are upregulated in the infarct. A dual gene delivery system was designed to target both extra- and intracellular areas of the ischemic heart by combining transactivating transcriptional activator peptide and monoclonal anti-myosin antibody 2G4 within a liposome carrier [40]. The complex was labeled with green fluorescent protein (GFP) and injected IV 30 minutes after occlusion of the coronary artery and infused for over 10 minutes. Accumulation and higher GFP expression were observed in the infarct up to 48 hours after injection compared to groups treated with liposomes complexed with a nonspecific antibody. In a separate study, liposomes labeled with angiotensin were injected IV into infarcted mice 1, 4, and 7 days post-MI, and accumulation was observed mainly in the left ventricle for all time points 24 hours post-injection [41]. Liposomes conjugated with a nonspecific peptide sequence were designed as a negative control, however accumulation was also observed when injected up to 1 week post-injury. These results suggest that while the system was designed to specifically target the angiotensin receptor post-MI, the therapeutic delivery is mainly due to the EPR effect.

Polymeric nanoparticles have also been explored for targeting the acute MI. For example, a peptide-polymer system targeting ischemic myocardium was developed using a peptide sequence that was identified via phage display to have a high affinity for infarcted myocardium [42,43]. The particles were composed of a cystamine bisacrylamide-diamino hexane polymer carrier conjugated with the ischemic myocardium targeted peptide (IMTP) for targeting and D-9-arginine (D9) for increased transfection. Following IV injection into a rat MI model 20 minutes after reperfusion, successful targeting to the damaged region and increased gene expression was shown. In another study, tetravalent streptavidin was used as the nanoparticle core, which was conjugated with biotinylated IGF and biotinylated PEG-Hoechst [44]. Hoechst binds to DNA, which is released as cells undergo necrosis in acute MI. After IV injection in a mouse MI model, the delivery of IGF to the infarcted region was significantly higher for the Hoechst-containing complex than the unlabeled control [45]. Improved heart function was also demonstrated 28 days after injection.

Conclusion

Using nanomaterials with minimally invasive strategies to treat MI may reduce debilitating, late stage effects of cardiovascular disease. Injectable hydrogel networks, such as ECM hydrogels or self-assembling peptides, form nanofibrous scaffolds that can facilitate endogenous cell infiltration or therapeutic delivery. A number of additional scaffolds have been designed to treat MI, but many have not been fully characterized to examine their nanoscale properties nor have they been investigated in an *in vivo* model. Intramyocardial delivery of nanofibrous hydrogels, nanoparticles, or in combination with therapeutic molecules localizes treatments to the site of injury using catheter or surgical based injections. By delivering the materials through a catheter, invasive surgical procedures may

be avoided, reducing patient recovery times and chance of infection. The infarct region is, however, unstable early after MI, and intramyocardial injections may increase the risk of ventricular rupture, resulting in safety concerns in acute MI patients. The concern using this approach may be addressed by delivery through IV injection or coronary infusion, as the leaky vasculature of the acute MI allows nanoparticles to enter the injured site. Hydrogel therapies are beginning to reach the clinic; however, translating nanoparticle therapies is likely to be a longer and more expensive process given the greater potential for off target effects [46]. The Food and Drug Administration recently issued guidelines for nanotechnology [8], which will be necessary to design safe and effective nanotherapeutics. Continued work and investment in this area, examining both safety and efficacy of the different materials and delivery approaches, will be critical to realize new nanomaterial based therapeutics for treating MI.

Acknowledgments

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Highlights

- Delivery of nanomaterials to treat MI has the potential for clinical application.
- Approaches for delivery include intracoronary, intramyocardial, and IV injection.
- Biomaterials explored to treat MI include nanofibrous hydrogels and nanoparticles.

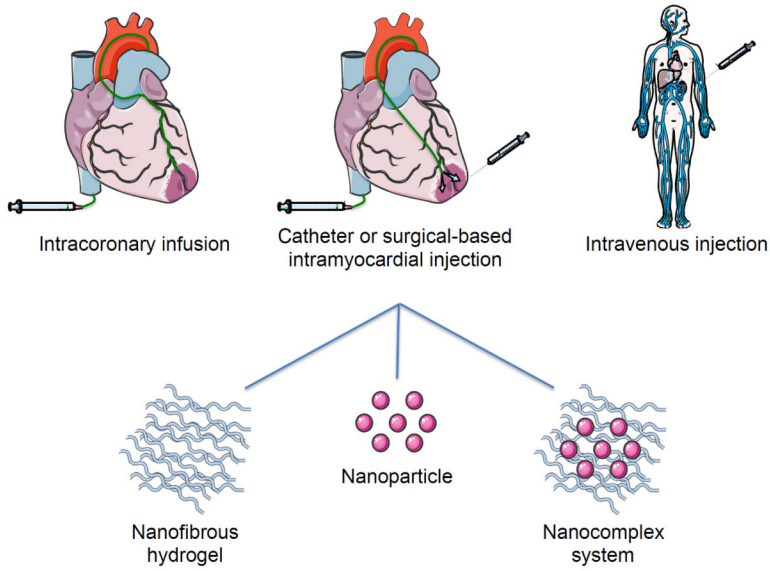

Figure 1.

Therapeutic delivery routes to the infarcted heart. Nanomaterials can be delivered to the heart through catheter-based intracoronary infusion, intramyocardial injection either via a transendocardial catheter or surgical-based direct injection, or through IV delivery and subsequent targeting to the site of infarction. Nanofibrous hydrogels or nanocomplexes have been delivered via intramyocardial injection, while nanoparticles have been delivered IV and have the potential for intracoronary infusion.

Table 1

Injectable nanomaterials for treating MI

Material	Dimensions	Therapeutic	Animal	MI model	Control	Results compared to controls	Reference
Surgical based injection of hydrogels							
SAP	5 nm fiber diameter	VEGF	SD rats and Lanyu minipigs	CAL	Saline, free VEGF, SAP alone	Increased neovascularization and improved cardiac function	[26]
SAP with heparin domain	10 nm fiber diameter	VEGF	SD rats	CAL	SAP alone, SAP with heparin domain, saline	Improved cardiac function, decreased infarct size, and increased angiogenesis	[27]
MA gelatin and PEI with GO nanosheets	30–40 nm nanosheets	VEGF-165 gene	Lewis rats	CAL	Hydrogel alone, hydrogel and VEGF-165, VEGF-165 alone, saline	Increased angiogenesis and cardiac function	[34]
Pericardial ECM	200 nm fiber diameter	bFGF	SD rats	I/R	ECM alone, bFGF in collagen, collagen, saline	Increased vessel density	[30]
Catheter based injection of hydrogels							
Cardiac ECM	100 nm fiber diameter	-	Yucatan minipigs	Percutaneous coil embolism	Saline, untreated	Improved global and regional cardiac function and ventricular volumes; increased cardiac muscle and reduced infarct fibrosis.	[31]
Ureido-pyrimidinone and PEG	75–100 nm fiber length	HGF and IGF	Dutch landrace pigs	Intracoronary balloon occlusion	Hydrogel alone, free HGF and IGF	Reduced infarct collagen content	[33]
Surgical based injection of nanoparticles							
PLGA	234 nm diameter	PGF	SD rats	CAL	Saline, free PGF	Improved cardiac function and reduced infarct expansion	[35]
PLGA	60 nm diameter (PLGA) 74 nm diameter (with IGF)	IGF	FVB mice	CAL	Saline, free IGF, nanoparticles alone	Improved ejection fraction and reduced infarct size compared to the saline and free PGF groups	[36]
IV delivery of nanoparticles							
Gd micelles or liposomes	15 nm diameter (micelle) 100 nm diameter (liposome)	-	Swiss mice	CAL	Gadopentetic acid	Improved accumulation of micelles to infarct area monitored through noninvasive imaging Improved heart function and vascular density	[37]
Liposomes	180 nm diameter	VEGF	SD rats	CAL	Free VEGF, liposomes only, no treatment		[38]
DDFT nanoparticles	250 nm diameter	Oxygen	C57BL/6J mice	CAL	Saline	Decreased infarct size	[39]
Myosin and TATp liposomes	170 nm diameter (liposome) 220 nm diameter (with TATp)	-	Rats	CAL	Liposomes with nonspecific Ab	Increased accumulation in infarct zone, increased transfection of cardiomyocytes	[40]
Ang-labeled liposomes	142 nm diameter	-	C57BL/6J mice	CAL	Nanoparticles labeled with nonspecific peptide	Successful targeting to infarct zone	[41]
IMTP-CD-9R nanoparticle	350 nm diameter	-	SD rats	I/R	Nanoparticles in healthy animals	Successful targeting to infarct zone, increased gene expression	[42]
PEG/Hoechst/Streptavidin nanocomplex	Dimensions not reported	IGF	Mice	I/R	Unlabeled complex, saline	Increased accumulation in infarct zone, improved heart function	[45]

Ang: angiotensin; bFGF: basic fibroblast growth factor; CAL: coronary artery ligation; CD: cystamine bisacrylamide-diamino hexane polymer; D9: D-9-arginine; DDFP: dodecafluoropentane; ECM: extracellular matrix; Gd: gadolinium; GO: graphene oxide; HGF: hepatocyte growth factor; I/R; ischemia/reperfusion; IGF: insulin-like growth factor; IMTP: ischemic myocardium-targeted peptide; MA: methacrylate; PEG: polyethylene glycol; PEI: polyethylenimine; PGF: placental growth factor; PLGA: poly(lactic-co-glycolic acid); SAP: self-assembling peptide; SD: Sprague-Dawley; TATp: transcriptional activator peptide; VEGF: vascular endothelial growth factor.