Nanoparticles for postinfarct ventricular remodeling

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In recent years, tremendous progress has been made in the treatment of acute myocardial infarction, but pathological ventricular remodeling often causes survivors to suffer from fatal heart failure. Currently, there is no effective therapy to attenuate ventricular remodeling. Recently, nanoparticle-based drug delivery systems are widely applied in biomedicine especially in cancer and liver fibrosis, owing to its excellent physical, chemical and biological properties. Therefore, the use of nanoparticles as delivery vehicles of small molecules, polypeptides, etc. to improve postinfarct ventricular remodeling is expected. In this review, we summarize the updated researches in this fast-growing area and suggest further works needed.

First draft submitted: 28 July 2018; Accepted for publication: 5 October 2018; Published online: 24 October 2018

Keywords: biomarker • drug delivery • engineering • extracellular vesicles • heart failure • inorganic nanoparticles • liposome • mechanism • myocardial infarction • postinfarct ventricular remodeling

With an aging population and the rising incidence of cardiovascular diseases (CVDs), such as hypertension and coronary heart disease, the prevalence of heart failure is gradually increasing. In 2013, 1 in 9 death certificates (284,388 deaths) in the USA mentioned heart failure, with heart failure being the primary cause in 58,309 of those deaths [1]. In China, the prevalence of heart failure is around 0.9%, and coronary heart disease is the major cause.

Primary myocardial damage (including ischemic myocardial damage like myocardial infarction and immune myocardium damage like myocarditis) and cardiac overload (including pressure overload and volume overload) can impair heart muscle, resulting in compensatory changes such as ventricular hypertrophy or ventricular enlargement, known as 'ventricular remodeling'. In this process, the heart's geometry, cardiomyocytes, interstitial components and the phenotype of cardiomyocytes undergo a series of pathological changes. Ventricular remodeling is the basic mechanism of heart failure and has three main characteristics: pathological cardiomyocyte hypertrophy accompanied by re-expression of embryonic genes, myocytes death, excessive fibrosis or increased degradation of myocardial extracellular matrix (ECM). In recent years, the molecular mechanism of ventricular remodeling has been studied mainly from the following aspects: myocardial hypertrophy, fibrosis, inflammation, mitochondrial dysfunction, autophagy/apoptosis. We may slow the progression of cardiac remodeling by targeting the above mechanisms, thus benefiting heart failure patients.

Nanoparticles refer to particles smaller than 100 nm in at least one dimension. Due to its small size and excellent thermal and electrical properties, nanoparticles are now widely applied into biomedical and industrial fields such as aerospace, electronics, cosmetics, food additives and optical devices [2]. Meanwhile, considering inherent nanometer size of living cells' biological components, nanotechnology is being considered in various medical fields such as oncology and cardiovascular medicine. Nanoparticles as delivery vehicles of proteins, nucleic acid and small molecules may potentially provide sustained treatment in damaged tissues. Basic research showed that nanoparticles packed with Nox2-NADPH oxidase siRNA, insulin growth factor-1 (IGF-1) or pitavastatin enhanced cardiac function post myocardial infarction (MI) [2–4], suggesting the infinite possibilities of nanoparticles in the treatment of postinfarct ventricular remodeling.

In this review, we first introduced the present understanding of mechanism of ventricular remodeling and new advances of drugs for ventricular remodeling, then focused on the most commonly used nanoparticles in CVD, especially for postinfarct ventricular remodeling. We also briefly touched on nanoparticles used as diagnostics/biomarkers for CVD, and engineering of nanoparticles for tailored and directed use, which are both growing rapidly in the area.

The mechanism of ventricular remodeling

Myocardial hypertrophy

Myocardial hypertrophy is a powerful adaptive form for various causes of cardiac output reduction, but it is not infinite. If pathological factors last for a long time, the function of the hypertrophic myocardium cannot be maintained persistently and eventually turns to heart failure. At present, plenty of studies support that apelin receptor (APJ receptor), a G protein-coupled receptor, plays a significant part in cardiac hypertrophy [5]. The hypothesis has been raised that APJ internalization via clathrin-mediated endocytic pathway may contribute to myocardial hypertrophy. As the molecular mechanisms of cardiac hypertrophy have been widely studied, the role of long noncoding RNAs has become more prominent [6]. The long noncoding RNA Mhrt (myosin heavy chain-associated RNA transcript) is shown to affect cardiac hypertrophy remodeling by affecting the acetylation of myocardin, a substance which is necessary for programming cardiac muscle [7].

Myocardial fibrosis

Myocardial fibrosis is known for excessive accumulation of ECM in the myocardium, which is a basic component for most cardiac pathologic changes [8]. Fibrotic cardiac muscle is stiffer and less compliant, causing ventricular systolic and diastolic dysfunction.

Changes in ECM components

Myocardial ECM is composed of collagen, proteoglycans, glycoproteins, glycosaminoglycans and elastic fibers, which are synthesized and secreted by cardiac fibroblasts. These components are essential for the nutrition and conduction of myocardium, and the normal structure and function of heart. Under the condition of ischemia and hypoxia, cardiac fibroblasts will move to the injured site, and produce a large amount of ECM under the mediation of various cytokines and neurohumoral factors. Epicardium-derived cells, but not bone marrow-derived blood cells, are the main origin of cardiac fibroblasts in the infarcted heart [9]. Significantly, differentiated states of fibroblasts are of importance to postinfarct ventricular remodeling of scarring. Fibroblasts were activated and highly proliferative, reaching a maximum rate within 2–4 days after MI. Up to 3–7 days, these cells differentiated into myofibroblasts and expressed smooth muscle α -actin to structurally construct the infarcted zone. As the scar completely formed (around 7–10 days), myofibroblasts gradually lost proliferative ability and smooth muscle α -actin expression [10]. This suggests that these fibroblasts might be a target of nanoparticle-mediated drug delivery system (DDS).

Matrix metalloproteinases (MMPs) are a family of zinc-dependent endopeptidases, which can degrade ECM. According to their structure and substrate selectivity, MMPs can be roughly classified into collagenase, gelatinase, matrix lysin, membrane-type metalloproteinase and others. Under normal conditions, MMPs are mostly in the form of zymogens, with low expression levels and weak activity. Once activated under the stimuli of various pathological factors, such as ischemia and hypoxia, MMPs rapidly participate in the degradation of ECM and modulate the signaling pathways related to vascular remodeling and myocardial fibrosis. It has been shown that elevated MMP-9 levels are associated with left ventricular dysfunction and targeted knockout of mouse *MMP-9* gene can decrease collagen accumulation post-MI and attenuate left ventricular dilation [11].

Disproportionality of myocardial collagen fiber

Fibrillar collagen is the major structural protein of cardiac ECM. It is generally classified into Type I (approximately 85%), Type III (about 11%) and quite less abundant Types IV, V and VI. Collagen Types I and III have their own functions, that is collagen Type I is responsible for building thick fibers which maintain its tensile strength, while collagen Type III is in charge of constructing thin fibers which keep elasticity of the matrix [12]. Changes in the number, distribution and arrangement of collagen fibers can lead to fibrosis. Cardiac fibroblasts are the major source of collagen fibers in the myocardial infarction. As the most frequently used marker of myocardial fibrosis, collagen peptides can predict cardiac function. For instance, the most common marker of Type I collagen is a 100 kDa, C-terminal polypeptide whose plasma levels are positively correlated with diastolic dysfunction; the most

commonly used marker for the synthesis of Type III collagen is a 42-kDa, N-terminal polypeptide, whose plasma levels are positively associated with mortality and heart failure [13,14].

Inflammation

Inflammation plays a vital role in ventricular remodeling, and its lasting activation may result in irreversible cardiac damage. Activation of multiple inflammatory factors and signaling pathways have been mentioned in patients with heart failure [15]. Inflammatory molecules involved in ventricular remodeling mainly include TNF- α , IL-6, IL-10, IL-18 and nuclear factor- κ B. Under the chemotaxis of multiple cytokines, monocytes are recruited to the cardiac tissue from circulation, and then they differentiate into macrophages and contribute to tissue injury and myocardial fibrosis [16]. Infarct macrophages exhibit inflammatory 'M1' phenotype early and reparative 'M2' phenotype later after MI [17]. Numerous studies have shown that the shift from M1 to M2 macrophages can improve postinfarct ventricular remodeling. Future studies can be aimed at targeting specific harmful functions while preserving beneficial effects of macrophages to prevent adverse cardiac remodeling.

NLRP3 inflammasome is a large molecule polypeptide complex, a component of the innate immune system. It is of great importance in both aseptic and infectious inflammation and can be activated by a variety of endogenous and exogenous factors. Studies have revealed that NLRP3 is closely associated with the pathogenesis of heart failure. When the myocardium is in a state of ischemia, NLRP3 is activated, producing IL-1 β and IL-18. IL-1 β further activates nuclear transcription factor (NF- κ B). In turn, activation of NF- κ B can also induce the expression of precursors such as IL-18 and IL-1 β . IL-18 is associated with the expression of collagen types I and III in a dose-dependent manner and induces myocardial remodeling and interstitial fibrosis.

Mitochondrial dysfunction

Mitochondrial dysfunction may potentially participate in almost all the mechanisms involved in ventricular remodeling [18]. Varieties of studies have demonstrated that there are functional defects of electron transport chain and oxidative phosphorylation complex in myocardial mitochondria during heart failure. In animal models of heart failure, the activity of myocardial mitochondrial complex IV is significantly reduced and the activity of complexes I and III are inhibited. These changes not only reduce mitochondrial ATP synthesis but also increase mitochondrial reactive oxygen species (ROS) production. ROS modifies the myofibrillar protein of the myocardium through oxidation, resulting in the progressive reduction of cardiac contractility and irreversible cardiac damage [19].

In addition, angiotensin II (Ang II) destroys myocardial mitochondria by increasing the production of ROS and interferes with mitochondrial oxidative phosphorylation, including fatty acid oxidation [18,20]. Fatty acids are the main energy substrate of the heart and offer most cofactors essential for mitochondrial oxidative phosphorylation. Studies have shown that overexpression of angiotensinogen in transgenic mice (TG1306/R1 mice) can reduce cardiac fatty acid oxidation and expression of PPAR α protein and fatty acid oxidase [21].

Autophagy & apoptosis

Autophagy is the decomposition process of proteins and organelles. It is characterized by the encapsulation of cytoplasmic proteins or organelles to form autophagosomes with a bilayer membrane structure. Autophagosomes fuse with lysosomes to form autolysosomes. The parcels are decomposed into small molecules such as free amino acids and fatty acids and be recycled [22]. Macroautophagy, microautophagy and chaperon-mediated autophagy all allude to autophagy, but here autophagy refers to macroautophagy [23]. Cardiomyocyte autophagy plays a prominent role in maintaining the stability of internal environment, and the structure and function of heart. Ischemia induces autophagy in cardiomyocytes. Kanamori first reported that autophagy was rapidly activated in cardiomyocytes within 30 min after coronary ligation, and strong autophagic activity was observed particularly in saved cardiomyocytes around the infarcted zone [24]. His following study found that autophagy inhibitor chloroquine can reduce myocardial autophagy and aggravate ventricular dilatation and myocardial remodeling, suggesting that autophagy plays a protective role in postinfarct ventricular remodeling [25]. There are two main pathways for the regulation of myocardial cell autophagy: mTOR-dependent pathway and Beclin1-dependent pathway. Among them, the mTOR-dependent pathway plays a major role in postinfarct ventricular remodeling. mTOR, a serine/threonine protein kinase, is proved to regulate autophagy. Increased mTOR activity inhibits autophagy while decreased mTOR activity activates autophagy [26].

Necrosis has been considered as the only cause of myocyte loss in MI for a long time. However, mounting evidence suggests that apoptosis plays a critical role in the progression of postinfarct ventricular remodeling and

Figure 1. The mechanism of ventricular remodeling. Hypertrophy, fibrosis, inflammation, mitochondrial dysfunction, autophagy and apoptosis are involved in the pathways of ventricular remodeling.

Table 1. New advances of drugs for ventricular remodeling.				
Classification	Typical Drugs	Function	Study	Ref.
RAAS inhibitors	Aliskiren, aldosterone, eplerenone	Inhibit cardiac hypertrophy and reduce the proliferation of extracellular matrix and interstitial fibrosis	Gheorghiade <i>et al.</i> Dhillon <i>et al.</i>	[32] [33]
β-Adrenoceptor blockers	Atenolol, metoprolol tartrate tablets, propranolol	Block the sympathetic nervous system, RAAS system and reduce oxygen consumption of heart muscle	Xie <i>et al.</i>	[34]
HMG-CoA inhibitors	Atorvastatin rosuvastatin	Inhibit oxidation and inflammation, reduce sympathetic nerve activity and improve vascular endothelial function	Duan <i>et al.</i> Mahalwar <i>et al.</i>	[35] [36]
Vascular endothelin-1 (ET-1) Receptor antagonists	Bosenta, enrasentan, tezosent, sitaxentan, atrasentan, ambrisentan	Contract blood vessels, promote cell mitosis and proliferation.	Prasad <i>et al.</i>	[37]
New vasodilators	Sildenafil, AVE9488	Inhibit cardiac hypertrophy, apoptosis and fibrosis	Vecchis <i>et al.</i> Fraccarollo <i>et al.</i>	[38] [39]

HMG-CoA: Hydroxy-3-methyl-glutaryl Coenzyme A; RAAS: Renin–angiotensin–aldosterone system.

heart failure, too. Cardiac-specific caspase-3 is the most important caspase in the terminal apoptotic pathway in the infarcted heart. The study found that overexpression of caspase-3 increased infarct size in transgenic mice [27]. Vice versa, reduced caspase-3 narrowed the infarct size, lowered the number of apoptotic cardiomyocytes and promoted the cardiac function in MI mice [28,29]. One study from Zhou *et al.* found that isoproterenol induces abnormal endoplasmic reticulum stress through inactivation of AMPK, which in turn damages cardiomyocytes, causes apoptosis and leads to heart failure in rats, and all the processes can be suppressed by activating AMPK, providing a potential mechanism of apoptosis [30].

In conclusion, none of the above processes is independent. On the contrary, they interact with each other and form a complex mechanism network. Nanoparticles loaded with the drugs targeting any of these mechanisms are expected to reverse ventricular remodeling and prevent further progression of the disease. We summarized the mechanism of ventricular remodeling in Figure 1.

Nanocargo for ventricular remodeling

Drugs, proteins, RNA and other small molecules all can be the cargo of nanoparticle-based DDS, which we describe below in details.

Drugs

We summarized new advances of drugs for ventricular remodeling in Table 1. The recent development of cardiovascular medicine and coronary intervention like PCI greatly decreased the mortality of acute myocardial infarction

Table 2. New advances of proteins for ventricular remodeling.

Proteins	Cardioprotective effect	Study	Ref.
VEGF	Promote cardiac stem cells differentiation into vascular endothelial cells	Xiao <i>et al.</i>	[41]
IGF-1	Promote stem cell growth and differentiation	Jackson <i>et al.</i>	[42]
Thymosin β 4	Promote neoangiogenesis and cardiac regeneration	Srivastava <i>et al.</i> Shrivastava <i>et al.</i>	[43] [44]
FAP- α	Promote fibroblast migration	Tillmanns <i>et al.</i>	[45]
HIF-1 α	Promote cardiac function, angiogenesis, cardiomyocyte proliferation and reduction of fibrotic tissue with no induction of cardiac hypertrophy	Cerrada <i>et al.</i>	[46]
Wnt1/ β catenin	Induces cardiac fibroblasts to proliferate and express pro-fibrotic genes	Duan <i>et al.</i>	[47]
TGF- β	Activate a pro-fibrotic and matrix-preserving program in infarct fibroblasts through Smad-dependent actions	Shinde <i>et al.</i>	[48]

FAP- α : Fibroblast activation protein α ; HIF-1 α : Hypoxia-inducible factor-1 α ; IGF-1: Insulin-like growth factor-1; TGF- β : Transforming growth factor β ; VEGF: Vascular endothelial growth factor.

(AMI), but the incidence of chronic heart failure patient's post-MI is increasing. Nanotechnology-based DDS (nano-DDS) is a hot topic in drug delivery and has been successfully adopted in cancer therapy. Besides higher biocompatibility, nano-DDS can increase the precision of drug targeting and the level of drug accumulation in the desired area, which will be discussed in detail in later sections. Therefore, nano-DDS has great potential in CVDs. As is known to us all, statins have anti-inflammatory effects. Katsuki *et al.* utilized PLGA as the carrier of Pitavastatin and tested its efficacy in MI model. They found intravenous treatment with PLGA-Pitavastatin nanoparticles attenuated postinfarct ventricular remodeling by interfering with monocyte recruitment and reducing monocyte/macrophage accumulation in the heart. This indicated that inflammatory cells might be the target of PLGA-Pitavastatin nanoparticles [31].

However, not all the drugs could be nanoparticulated in view of their size and structure. Furthermore, there are few animal studies using nanoparticles in the treatment of heart diseases, albeit clinical trials. For example, Zhang *et al.* showed size-dependent cardiac effects of gold nanoparticles (AuNPs) in isoproterenol-induced hyperthyroid rats, suggesting that size is an important factor affecting safety and efficacy of nano-DDS [40]. Further extensive work is needed to explore the target cells and examine the efficacy and safety of these cardioprotective drugs with nano-DDS before going into clinical trials.

Proteins

We summarized some proteins which contribute to cardiac repair and attenuate adverse remodeling in Table 2. Under ischemic conditions, certain proteins can play important roles in attenuating and delaying pathological ventricular remodeling. However, their effect is quite limited as a result of short half-lives *in vivo* in their free form. What if they are nanoparticulated? In fact, some of them have been nanoparticulated for use in the treatment of postinfarct ventricular remodeling in animal experiments. For example, injecting PLGA-IGF-1 nanoparticles into the myocardium of MI mice was effective to narrow infarct size, prevent cardiomyocyte apoptosis and improve left ventricle ejection fraction 3 weeks after the left coronary ligation surgery [3]. But similar animal studies are still lacking, and transition from basic research into clinical trials is near to zero. Future studies should focus on this part of works and provide more reliable data.

Ribonucleic acid

miRNAs are small, noncoding, single-stranded RNAs, which can regulate the gene expression by interacting with target mRNAs and preventing them translating into functional proteins. It has been shown that *miR-1*, *miR-21*, *miR145*, etc. modulated the gene expression relative to ventricular remodeling. If these miRNAs are nanoparticulated and delivered to the infarcted heart, it may prevent adverse ventricular remodeling. In fact, extracellular vesicles (EVs) are natural delivery vehicles of miRNA and have been used in the treatment of ventricular remodeling in basic research, which will be discussed in detail in later part. Other kinds of nanoparticles such as liposomes are also studied. For example, one study investigated that *miR-145* encapsulated in liposomes was intravenously administered to MI rabbit and had a cardioprotective effect by inducing cardiomyocyte autophagy through targeting fibroblast growth factor receptor substrate 2 [49].

Small hairpin RNA, an artificial RNA, is named for a tight hairpin turn that can be used to silence specific gene expression through RNA interference and reduce the level of targeted proteins. As an example, one study exhibited that rPEI/siRAGE showed high target gene silencing and low toxicity in cardiomyocytes, and the treatment of rPEI/siRAGE reduced the myocardial infarction size [50].

Nanoparticles for treatment of postinfarct ventricular remodeling

Heart failure post-MI is an important component of cardiovascular related diseases. As mentioned before, the repair mechanism of post-MI causes collagen scarring to replace damaged cardiomyocytes. The nonshrinkage of the scar leads to viable cardiac hypertrophy, thinning of the infarct wall and expansion of the ventricles, which is known as ventricular remodeling. Without effective treatment, these processes will continue until the heart no longer adequately pumps enough blood to the body, which is defined as heart failure. At present, the drugs used for the treatment of heart failure only aim at its pathophysiological process, but do not target the cause. Worse still, the current available means of delivering cardioprotective drugs often misses the deadline of reversible repair of cardiomyocytes and inevitably, cardiomyocytes undergo a series of remodeling processes. Therefore, developing novel therapies to alleviate the negative left ventricular remodeling post-MI is very important.

Nanoparticles refer to nanometer-sized particles. It is defined as particles smaller than 100 nm in at least one dimension. Due to its small size and excellent thermal and electrical properties, nanoparticles are now widely used in industrial and biomedical fields such as cosmetics, food additives, aerospace, electronics and optical devices [2]. Considering the intrinsic nanometer size of the living cell's biological components, if nanoparticles are designed as delivery vehicles of a variety of growth factors, enzymes and small molecule, the modified nanoparticles may provide infinite possibilities in the treatment of CVDs. In addition, nanoparticles can achieve controlled drug release by constructing a release system in response of internal stimuli such as pH, redox state and the presence of biomolecules as well as external stimuli such as light and magnetic field. One study showed that pH-sensitive mesoporous silica-based nanoparticles could be mostly taken up by tumor cells for their acidic environment due to hypoxia [51]. Similarly, an infarcted heart is also in an acidic environment under ischemic condition. pH-sensitive nanoparticles can also be designed to achieve controlled drug release. In addition, if the nanoparticles can only be opened by specific enzyme which is limited to infarct heart, the controlled drug release can also be achieved. Currently, the most commonly used nanoparticles in cardiovascular research are inorganic nanoparticles, liposomes and EVs, which are discussed below.

Inorganic nanoparticles

Common inorganic nanoparticles include AuNPs, silver nanoparticles and silicon nanoparticles and so on. They are widely studied in basic research associated with CVDs.

Gold nanoparticles

AuNPs have great potential in the diagnosis and treatment of various diseases, owing to their superior physicochemical and pharmacological characters. In terms of physicochemical properties, AuNPs are inert, stable and biocompatible, which means low toxicity. Moreover, the surface of AuNPs can be retouched as we wish, to improve precision and safety of its application in clinical or research [52]. As for the preparation process, AuNPs are easy to prepare and functionalize, which may lower the production cost, and this obvious economic advantage will make them more available in clinical. Based on the above, AuNPs are a valuable candidate for many biomedical applications, such as drug delivery, cancer therapy and biomedical imaging. This part focuses on the previous studies of AuNPs in drug delivery. One study showed that continuous injection of gold nanofibers combined with platelet-derived growth factor into the heart of rats could reduce myocardial cell death and maintain systolic function post-MI. Considering that heart failure is related to abnormal electrical function, modified nanofibers to couple the electrical property was studied. The result showed that *ex vivo* pretreatment of mesenchymal stem cells (MSCs) using 5-azacytidine and AuNPs loaded with conductive nanofibrous construct could improve cardiomyogenic differentiation, thus resulting in protective effects on infarcted area [53]. Another study showed that PEG-coated AuNPs could attenuate β -adrenergic receptor-mediated acute cardiac hypertrophy and inflammation by inhibiting the expression of β 1-AR and its downstream effectors IL-6 and ERK1/2 [52]. In conclusion, AuNPs have at least two functions for treating heart failure: one is used as drug vector and the other is used as anti-cardiac hypertrophy agents.

Silicon nanoparticles

Silicon nanoparticles are also drawing more and more attention. Porous silicon (PSi) shares the similar characters with AuNPs such as nanoscale size, large surface area ($> 300 \text{ m}^2/\text{g}$) and good biocompatibility and biodegradability [54,55]. Besides, high degree of porosity (50–80%) and the unique chemical surface are two special features of PSi, which can promote the solubility of hydrophobic drugs and control the drug release. An *in vivo* experiment tested the biocompatibility of different sizes of thermally oxidized PSi nanoparticles in the heart tissue. Obvious changes in cardiac function and other systems like the hematological system were not found before and after MI, demonstrating that thermally oxidized PSi nanoparticles have good biocompatibility [56]. Other research concluded that functionalized undecylenic acid thermally carbonized PSi nanoparticles can improve their ability of accumulation in different cardiomyocytes (primary cardiomyocytes, noncardiomyocytes and H9C2 myocardium). It has also been reported that intravenous administration of peptide-modified nanoparticles in MI rats induced by isoproterenol, could increase the accumulation of nanoparticles in the heart up to 3.0 times in 10 min, revealing the potential therapeutic effect of these peptide-modified nanosystems in postinfarct ventricular remodeling. Therefore, we can confidently expect that the PSi materials modified with heart-targeting peptides and cardioprotective factors might serve as a promising approach to treating heart diseases.

Nanoparticles mentioned above are delivered by directly injecting into the infarcted heart or through the intravenous administration. Some studies also deliver nanoparticles orally. However, this route of administration can cause an undesirable systemic response for their inherent metabolic pathways. Currently, drug delivery using inhaled nanoparticles has demonstrated a promising future [57–59]. For example, inhalation of calcium phosphate nanoparticles bound to peptides targeting heart were investigated and no changes in blood pressure, heart rate or respiratory function were observed [58]. Therefore, efforts to develop tailored approaches with engineering designs are a hot topic in the study, as described in part ‘engineering precision nanoparticles for personalized CVDs’.

It is worth noting that inorganic nanoparticles can also cause toxic effects in multiple organs. Experiments conducted on murine macrophage cell lines have shown that AuNPs could affect the immune system. In this study, AuNPs successfully reduced activation of Toll-like receptors-9 receptors, which in turn reduced the secretion of various interleukins (IL-6, IL-12) and TNF- α [60]. Silica nanoparticles can cause toxic effects, too. The elevated level of pro-inflammatory cytokines like IL-6 and IL-12, increased inflammatory cells such as natural killer cells and cytotoxic T-cells and upregulated genes associated with inflammatory responses were observed when cells were exposed to silica nanoparticles [61]. Besides, the level of cardiac muscle troponin (cTnT), a sensitive indicator of AMI, was significantly elevated in old rats exposed to aerosol of silica nanoparticles [62], which exhibited cardiotoxicity.

Liposomes

Liposomes are composed of single or multiple outer lipid bilayers and an inner aqueous compartment, thus endowed with special properties that can be combined with both hydrophobic and hydrophilic materials. The diameter of liposomes is usually 20–100 nm, and the thickness of phospholipid bilayer is around 4–5 nm. Microfluidic technology has gradually been employed for liposome preparation in place of conventional methods [63–65]. At present, PLA, PGA and PLGA are three popular materials for the preparation of liposomes. Initially, liposomes were used in surgical implants and tissue repair. They were then rapidly introduced into other medical fields such as abdominal mesh and drug-delivery vectors due to their excellent biocompatible, biodegradable and nontoxic properties [66–68]. Another unique advantage of using PLA to make nanoparticles is flexibility. Its physical properties as well as chemical properties are easily changed to obtain the desired pharmacokinetics and biodegradable properties [68,69]. Nanoliposomes have been shown to transport many substances such as low molecular weight drugs, imaging agents, peptides, proteins and nucleic acids. They can slowly release the encapsulated drug, maintain a higher drug concentration in the target area, and increase drug efficacy. This ability can also be applied to delivery of cardioprotective agents to the infarcted heart.

Ribonucleic acid

Nox2-NADPH, the major source of ROS in the heart, is associated with ventricular remodeling. It has been reported that the expression of Nox2-NADPH is upregulated in the infarcted myocardium and deleting the gene of *Nox2* can reduce oxidative stress and prevent adverse postinfarct remodeling. Considered above, a study used acid-degradable polyketal particles as delivery vehicles for *Nox2-siRNA* and found that intramyocardial injection of *Nox2-siRNA* nanoparticles to the post-MI heart successfully prevented upregulation of *Nox2* and dramatically improved cardiac function [2].

Proteins & peptides

A study reported that the amount of angiotensin II Type 1 (AT1) nanoliposomes clustered in the infarcted heart after day 1 accounted for almost half of the total amount accumulated in all organs, exhibiting superior cardiac-targeted capability [70]. IGF-1, a kind of peptide, has been revealed to improving cardiomyocyte growth and survival both *in vitro* and *in vivo*. An animal experiment showed that injecting PLGA-IGF-1 nanoparticles (NPs) into the myocardium of MI mice was effective in narrowing infarct size, preventing cardiomyocyte apoptosis and improving left ventricle ejection fraction 3 weeks after the surgery [3].

Drugs

It is well known that inflammatory responses play a critical role in the development of postinfarct remodeling [71]. For this reason, a study explored the effects of PLGA NPs combined with the anti-inflammatory drug-pitavastatin on post-MI mice and concluded that treatment with PLGA-pitavastatin NPs alleviated postinfarct remodeling along with a reduction of monocytes/macrophages in the heart, yet the control group did not. Specifically, PLGA-pitavastatin NPs not only prevented monocytes from mobilizing in the spleen in MI mice, but also decreased the amount of inflammatory cells in the infarcted heart in splenectomy mice [4]. This suggests that nanoparticles loaded with pitavastatin or other similar drugs may be a novel therapeutic strategy to protect the heart from inflammatory damage.

Compared with inorganic nanoparticles, there are few reports about the toxicity of liposomes. Lutein-PLGA nanoparticles were prepared and tested for acute, subacute toxicity, bioavailability and tissue distribution in mice. The results did not show any significant changes in mortality, hematology and other vital organs compared with the control group [72]. However, long-term toxicity studies are needed.

Extracellular vesicles

EVs, which are of nanoscale size and surrounded by a phospholipid bilayer, are secreted by almost all cell types into extracellular space. EVs are originally considered as cellular debris, but more value in carrying and exchanging biological information is explored with the in-depth research. According to the vesicles' size, biogenesis and surface markers, EVs can generally be divided into exosomes, microvesicles/ectosomes and apoptotic bodies. Exosomes, roughly 30–100 nm in size, are derived from late endosomes. Microvesicles, ranging between 100 and 1000 nm, are generated by budding from the plasma membrane. Apoptotic bodies are derived from apoptotic cells and are more than 1000 nm in diameter. However, due to the different methods of isolating and purifying vesicles, it is difficult to classify EV precisely. Clinical applications of EVs fall into two main categories: first, EVs are used as biological drugs. Some of the molecules contained in EVs secreted by specific cells have therapeutic effects such as immunosuppression, immune activation, tissue repair and cardiac protection [73]. Second, EVs are used as the drug-delivery system. EVs can serve as a natural nano-DDS to deliver drugs to target cells. Currently, EVs have been used successfully as a carrier for the delivery of small molecules, siRNAs, proteins and mRNAs for preclinical studies.

One study surprisingly found that although there are many kinds of cells in the heart tissue such as cardiomyocytes, endothelial cells and fibroblasts, EVs from CD34⁺ stem cells were only selectively captured by cardiomyocytes and endothelial cells, indicating the existence of cell-specific receptors on EVs from CD34⁺ stem cells [74]. Increasing evidence has confirmed that EVs are enriched in miRNAs, which regulate growth, proliferation and survival. More interestingly, miRNAs enclosed in different EVs are quite different from each other and perform different tasks. It has been demonstrated that cardiac progenitor cell-derived exosomal particles which contain *miR-21* could prevent cardiomyocytes apoptosis [75]. Other similar studies investigated that *miR-132* containing exosomes derived from pericyte had a pro-angiogenic capacity and *miR-155* containing exosomes could mediate macrophage-fibroblast interactions and protect damaged myocytes by inhibiting fibroblast proliferation [76]. All of these highlight that understanding how EVs are released and taken up would help to manage and govern postinfarct ventricular remodeling. Future studies might aim at targeted delivery of EVs containing beneficial factors to heart. We summarized the latest findings of exosomes and their miRNAs on cardiac repair in Table 3.

Compared with liposomes, EVs have the following characters: EVs contain a lipid layer and have a better fluidity; membrane proteins contained in the lipid layer of EVs are potentially targeted; EVs can be modified to carry the required membrane fusion and cell-uptake devices; EVs are similar to the body's own cells, so they are non-immunogenic and biocompatible; and EVs are self-cell products which can avoid being degraded by macrophages, endosomal and lysosomal pathways. These natural features make EVs easier to be captured by target

Table 3. Exosomes and the miRNAs on cardiac repair.

Cellular origins of exosomes	Contained miRNAs	Mechanism	Cardioprotective function	Study	Ref.
Cardiac-derived progenitor cells	miR-1	Target and inhibit the expression of sprouty-related EVH1 domain-containing protein 1 (Spred1)	Enhance angiogenesis and potentially improve cardiac regeneration	van Mil <i>et al.</i>	[77]
Induced pluripotent stem cells (iPS cells), derived from somatic cells reprogrammed by four stem cell transcription factors, Oct4, Sox2, Klf4 and c-Myc	miR-21, miR-210	Associate with Nanog, an embryonic stem cell-specific transcription factor and the key hypoxia related transcription factor HIF-1 α .	Reduce oxidative stress and promote cardiomyocytes survival	Wang <i>et al.</i>	[78]
MSC overexpressing GATA-4	miR-19a, miR-451	Activate the Akt and ERK signaling pathways	Reduce apoptosis	Yu <i>et al.</i>	[79]
Human CD34 ⁺ peripheral blood-derived hematopoietic stem cells	miR-126, miR-130a	Increase production of CXCL12 in endothelial cells and reduce protein levels of phosphoinositol-3 kinase regulatory subunit 2 (PIK3R2)	Promote angiogenesis	Mocharla <i>et al.</i>	[80]
MSCs	miR-22	Target methyl CpG binding protein 2 (MeCP2)	Reduce apoptosis and cardiac fibrosis	Feng <i>et al.</i>	[81]
SVP progenitor cells	miR-132	Inhibit Ras-GTPase activating protein and methyl-CpG-binding protein 2	Improve contractility, reparative angiogenesis and interstitial fibrosis	Katara <i>et al.</i>	[82]

MSC: Mesenchymal stem cell; SVP: Saphenous vein-derived pericyte.

cells and enhance drug delivery efficiency, opening up new ways for drug delivery. However, there is still a long way to fully master physiological characteristics of EVs and improve EVs isolation and drug loading techniques, finally realizing the changes from basic to clinical practice.

Nanoparticles used as diagnostics & biomarker for CVD

Nanoparticles are increasingly being recognized as markers of disease presence and prognosis like cancer and CVDs [83,84]. Previously noted, EVs are produced by budding from cytoplasm. Therefore, their contents indirectly reflect the type and condition of original cells. By detecting EVs in the serum, urine and other bodily fluids, we may identify the disease presence and evaluate prognosis. For instance, hypoxia and oxidative stress altered the proteomic and RNA content of endothelial and mast cells [85]. Increased microvesicle levels were found in acute coronary syndrome than that in stable angina [84]. Some clinical research suggested that plasma levels of exosomes subtypes might be used as indicators of vascular endothelium damage in CVD, but more work needed in exploring the potential and attractive ability of EVs.

Engineering precision nanoparticles for personalized CVDs

Current efforts in nanoparticle work develop increasingly toward tailored approaches and for this purpose nanoparticles, including EV therapy for heart disease, are being modified more and more, such as enzyme prodrug therapy and microfluidic technology. Enzyme prodrug therapy makes it possible to release drugs in desired positions by converting inactive prodrugs to active drugs with the participation of enzymes [86]. Microfluidic extrusion approaches for fabricating exosome mimetics from donor cells and microfluidic surface engineering of living-cell-derived exosomes are two research direction in microfluidic technology, but still face lots of challenges [87]. Magnetically sensitive microcapsules have provided a novel method of targeted cell delivery. Magnetically sensitive cells which contain magnetic nanoparticles in their walls can transfer to the desired sites and repair the damaged tissue in applied magnetic field [88]. However, there is almost no research on the application of magnetic sensitive microcapsules to CVDs.

Conclusion

CVD is one of the leading causes for death. Although great advances in therapy strategies have been achieved in AMI in recent years, pathological ventricular remodeling often causes survivors to suffer from fatal heart failure. Nanoparticles as emerging drug-delivery vehicles are drawing more and more attention, especially in cardiovascular areas. In this review, we summarized current knowledge about nanomedicine for postinfarct ventricular remodeling, and described basic mechanisms of ventricular remodeling, including hypertrophy, fibrosis, inflammation, mitochondrial dysfunction, autophagy and apoptosis. A better understanding of the mechanisms would help us to find

new therapeutic targets for ventricular remodeling. We also listed potential nanocargo such as drugs, proteins and RNA for postinfarct ventricular remodeling. Once nanoparticulated, these drugs, proteins and RNA might have better cardioprotective effects. Furthermore, we summarized the characteristics of inorganic nanoparticles, liposomes and EVs and listed their application in postinfarct ventricular remodeling. Nanoparticle-based DDSs show high compatibility, low toxicity, high drug accumulation and controllable drug release. To broaden the knowledge of nanomedicine, we also briefly described the engineering of nanoparticles.

Future perspective

To date, nanoparticles packed with peptides, siRNA and other small molecules are observed to exert beneficial effects on damaged cardiac myocytes and the infarcted heart both *in vitro* and *in vivo*. What is more, nanoparticles are shown to be potential biomarkers of CVD. Nonetheless, there are still some problems in the application of nanoparticles for treating postinfarct ventricular remodeling. First, nanoparticles lack specific markers for targeting cardiac myocytes. It can cause drug accumulation in other relevant target organs and correspondingly produce toxic and side effects. Second, the study of nanoparticles for improving cardiac remodeling is lacking the combination of long-term and short-term animal experiments. The commonly accepted method for establishing the model of AMI in rats is left anterior descending artery ligation. The surgery is very demanding on the operator's skill and is extremely traumatic for rats. Therefore, the long-term survival rate of rats (more than 3 weeks) is quite low. The future work should focus on the long-term animal experiments and investigate the long-term effects of nanoparticles to the infarcted animals. Third, there are few studies on the effects of nanoparticles on ion channels in cardiac myocytes. The ion channel is a popular and challenging topic in cardiac research. Do nanoparticles affect the ion channels in cardiac myocytes? If yes, what is the mechanism? This may be a direction for future research on nanoparticles. Fourth, there is still great technical difficulty and cost concerns in the manufacturing of ideal combination of drugs and nanoparticles. The nanoparticles need to be well engineered to achieve desired size, shape, surface charge and other physicochemical properties, thus a complex and costly method is demanded. Incomplete characterization of nanoparticles can lead to various biological effects. In addition, materials with combination of less toxicity and side effects, better biocompatibility and more controllable drug release will pose major challenges to the materials industry. Fifth, nanoparticles for the treatment of postinfarct ventricular remodeling are still lacking clinical data. Current research in this area is still limited to animal and cell experiments and there are no reliable clinical trials to support the idea. More work is urgently needed to achieve clinical transition of nanoparticles. 3D printing has gained a significant focus in biomedical and nanobiomaterials research. Future studies may adopt 3D printing technology in nanoparticle-based DDSs.

On a positive note, nanoparticles as the delivery vehicle of various drugs have already entered clinical research for the treatment of hepatic fibrosis and cancer. This brings hope to nanoparticles for postinfarct ventricular remodeling.

Executive summary

- The prevalence of heart failure is gradually increasing and ventricular remodeling is the major cause.
- Nanoparticles have great potential as drug delivery vehicles in postinfarct ventricular remodeling.

The mechanism of ventricular remodeling

- Hypertrophy, fibrosis, inflammation, mitochondrial dysfunction, autophagy and apoptosis are the basic mechanisms of ventricular remodeling.

Nanocargo for ventricular remodeling

- Nanoparticulation of drugs, proteins and RNA is expected to treating postinfarct ventricular remodeling.

Nanoparticles for treatment of postinfarct ventricular remodeling

- Inorganic nanoparticles, liposomes and extracellular vesicles as delivery vehicles of RNA, protein, drugs, and so forth, have been studied in basic research in the treatment of postinfarct ventricular remodeling.

Nanoparticles used as diagnostics & biomarker for cardiovascular diseases

- Nanoparticles are increasingly being recognized as markers of presence and prognosis of cardiovascular diseases.

Engineering precision nanoparticles for personalized cardiovascular diseases

- Enzyme prodrug therapy and microfluidic technology increase the precision of targeting.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

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