Nanoparticle and Exosome-Based Targeted Drug Delivery Systems for Atherosclerosis Diagnosis and Treatment: Opportunities and Challenges (Postprint)

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Abstract

Atherosclerosis is a chronic inflammatory disease in which atherosclerotic plaques chronically accumulate and obstruct the intima of large- and medium-sized arteries, leading to severe stenosis and circulatory impairment that precipitates tissue and organ ischemia and hypoxia. Nanomedicines have attracted considerable attention in atherosclerosis therapy due to their distinct advantages over conventional pharmaceuticals. This review focuses on several nano-targeted particle (systems) and exosome-targeted drug delivery systems for anti-atherosclerosis applications, briefly describing the synthesis processes of representative nanomaterials, analyzing their targeting capabilities, and summarizing both the benefits and inherent challenges of nanomedicines. Despite challenges requiring resolution and optimization, nano-targeted particle and exosome-targeted drug delivery therapies demonstrate promising prospects and hold potential for expanded clinical translation.

Full Text

Preamble

Opportunities and Challenges of Targeted Drug Delivery Systems of Nanoparticles and Exosomes for the Diagnosis and Treatment of Atherosclerosis

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Abstract Atherosclerosis is a chronic inflammatory disease characterized by the chronic accumulation of atheromatous plaques that obstruct the intima of medium and large arteries, leading to severe stenosis and blood flow disorders that cause tissue and organ ischemia and hypoxia. Nanomedicines have attracted widespread attention for their unique advantages over conventional drugs in treating atherosclerosis. This article focuses on reviewing several nano-targeted particle (systems) and exosome-targeted drug delivery systems in anti-atherosclerosis research, briefly describes the synthesis of representative nanomaterials, analyzes their targeting properties, and outlines the benefits and inherent challenges of nanomedicines. Despite challenges that need to be addressed and refined, nanoparticles and exosome-targeted drug delivery therapies hold great promise and are expected to be more widely applied in clinical practice.

[**Keywords**] atherosclerosis; nanoparticles; exosomes; inflammation; targeted therapy

Cardiovascular diseases represent the highest morbidity and mortality worldwide. As the pathological basis for most cardiovascular diseases, atherosclerosis is a chronic inflammation-induced disease characterized by thickening of arterial walls. Endothelial cell dysfunction initiates a vicious cycle that promotes vascular smooth muscle cell proliferation and extracellular matrix remodeling, ultimately leading to atherosclerotic plaque formation. Elevated low-density lipoprotein in plasma is one of the major factors driving plaque progression. Current treatments for atherosclerosis include lipid regulation, antiplatelet aggregation, and thrombosis inhibition. Statins are the cornerstone of pharmacotherapy for dyslipidemia and play an important role in preventing and controlling atherosclerotic cardiovascular disease both domestically and internationally; however, statin intolerance (at conventional doses) frequently leads to myopathy in clinical practice [1, 2]. To reduce adverse drug reactions and improve therapeutic efficiency, exploring novel drug delivery forms to intervene in atherosclerosis is of significant importance.

The combination of nanotechnology and medicine shows broad application prospects. With the rapid development of nanotechnology, nanocarrier-based drug delivery systems have attracted extensive attention. Nanotechnology offers several advantages for atherosclerosis treatment, including increased systemic drug circulation time, reduced off-target cytotoxicity, improved drug solubility, decreased required dosage, integration of diagnostic and therapeutic agents into theranostic platforms, and enhanced drug accumulation at specific sites [3]. In recent years, various industrial nanoparticles and engineered drug-loaded exosome-targeted delivery platforms have been reported, including dendritic macromolecules, micelles, immunoliposomes, macrophage-biomimetic

nanoparticles, DNA-coated nanoparticles, and red blood cell-based core-shell structured nanocomplexes for targeted drug delivery in atherosclerosis diagnosis and treatment [4-8]. Their delivery efficiency depends on size, shape, surface parameters, hydrophobicity, and biophysical-chemical properties [9]. Additionally, toxicity issues require further investigation to ensure clinical safety. This review summarizes several representative targeted delivery platforms developed in recent years and analyzes their structural characteristics, opportunities, and challenges in atherosclerosis diagnosis and treatment.

1. Literature Search Strategy

We searched the English databases PubMed and Web of Science (WOS) with a timeframe from January 1, 2007, to November 1, 2022. Search terms included "nanoparticle"and "atherosclerosis,""exosomes"and "targeted therapy,""atherosclerosis" and "exosomes," and "nanoparticle" and "targeted therapy." Inclusion criteria comprised high-quality literature on the mechanisms and efficacy of nanoparticle and exosome-targeted therapy for atherosclerosis. Exclusion criteria included studies unrelated to atherosclerosis-targeted therapy, low-quality research, and duplicate studies. Ultimately, 61 articles were included.

2. Application of Nano-Targeted Imaging Strategies in Atherosclerosis Diagnosis

Current primary imaging techniques for atherosclerosis include intravascular ultrasound (IVUS), computerized tomography (CT), positron emission computed tomography (PECT), perfusion-weighted imaging (PWI), and magnetic resonance imaging (MRI). Although these imaging techniques represent important advances in evaluating atherosclerotic plaque status, more targeted and precise strategies are needed to further improve treatment outcomes as medical technology evolves. Nano-targeted drug delivery systems offer new hope for efficient atherosclerosis diagnosis, as synthesized targeted nanoparticles can be introduced as novel contrast agents into conventional imaging systems to develop nano-targeted imaging platforms.

2.1 MRI-Based Nano-Targeted Imaging Platform

Nandwana et al. [10] synthesized "high-density lipoprotein-like magnetic nanostructures" (HDL-MNS) by adding phospholipids and apolipoprotein A1, which defines high-density lipoprotein, to the surface of magnetic nanostructures to mimic natural HDL particles. In imaging efficacy, HDL-MNS demonstrated a contrast enhancement in 7 T magnetic resonance imaging ($r2 = 383\ mM^{-1}s^{-1}$) five times greater than that of the T2 MRI contrast agent Ferumoxytol. Furthermore, HDL-MNS functioned identically to natural HDL in promoting cholesterol efflux and achieved comparable excretion efficiency. Oumzil et al. [11] loaded iron oxide particles and the antiplatelet aggregation agent prostacyclin onto solid lipid nanoparticles (SLN) for image-guided therapy. In imaging, SLN ex-

hibited a 4.7 T magnetic resonance signal (r2 = 557 $mM^{-1}s^{-1}$) 2.6 times stronger than the clinically used contrast agent Feridex® [11].

Given recent developments, introducing nano-iron oxide into MRI provides new solutions for atherosclerosis diagnosis. Most preclinical iron oxide nanoparticles demonstrate superior MRI contrast compared to commercial iron oxide MRI contrast agents such as Feridex®, FeREX®, and Resovist® [12]. Moreover, iron oxide nanoparticles can enhance targeting flexibility for specific cells or tissues by conjugating with histological reagents, antibodies, and transfection agents. Overall, nano-iron oxide will remain a primary research direction for future magnetic resonance imaging.

2.2 Fluorescence-Based Nano-Targeted Imaging Platform

In addition to MRI, fluorescent agents are commonly used to locate and detect atherosclerotic lesions. Lu et al. [13] developed photodynamic selenium nanoparticles (SeNPs) targeting inflammatory macrophages. In vitro studies showed that SeNPs provided stronger Rb fluorescence signals in lipopolysaccharide (LPS)-stimulated macrophages compared to unstimulated macrophages. Phototoxicity studies demonstrated that SeNPs could kill activated macrophages in a catalase-dependent manner while effectively reducing H2O2 levels in LPS-stimulated macrophages by 85.2%.

In another study targeting macrophages with therapeutic nanoparticles, Kosuge et al. [14] designed single-walled carbon nanotubes (SWNT) functionalized with Cy5.5 dye for near-infrared imaging of inflammatory macrophages. In vivo near-infrared imaging revealed strong near-infrared signals in the ligated left carotid arteries of mice treated with SWNTs, whereas no signals were detected in untreated mice.

Traditional fluorescence theranostic platforms have been hindered in biomedical applications due to poor imaging accuracy and limited deep-treatment efficacy. In contrast to conventional visible light (400–700 nm), near-infrared fluorescence platforms (NIR, 700–1400 nm) can significantly improve fluorescence imaging clarity and resolution, while NIR-II photothermal therapy substantially enhances treatment efficacy for deep-seated diseases. Future NIR photothermal fluorescence theranostic platforms will become one of the hot research directions in fluorescence-targeted platform development.

2.3 CT-Based Nano-Targeted Imaging System

Peter Chhour et al. [15] synthesized gold nanoparticles (AuNP). In in vivo animal experiments, gold-labeled primary monocytes were injected into apolipoprotein E-deficient mice fed a Western diet for 10 weeks. Imaging with a micro-CT scanner showed significantly increased attenuation in the aortas of mice receiving gold-labeled cells compared to controls. Furthermore, plaque sectioning and electron microscopy validation confirmed that AuNPs could target monocytes within plaques.

Jinbao Qin et al. [16] developed a facile method to synthesize non-toxic, biocompatible gold nanorods (Au-NRs) for efficient in vitro and in vivo imaging and photothermal ablation of macrophages. Micro-CT imaging of macrophages showed concentration-dependent signal intensity increases. In vivo thermotherapy in ApoE^{-}/$^{-}$ mice demonstrated slightly enhanced CT intensity in inflamed femoral arteries after intravenous Au-NR injection. This nanosystem has proven non-toxic and shows promise as a novel platform for atherosclerosis diagnosis and treatment.

However, CT imaging technology inherently involves radiation exposure, making multiple scans in short timeframes unlikely in clinical practice. Future development directions will focus on low-radiation, high-sensitivity, and high-targeting nanoparticles.

3.1 Factors Affecting Drug Delivery Efficiency

Nano-delivery systems are at the forefront of anti-atherosclerosis therapeutic development. In recent years, researchers have designed nanoparticles as delivery vehicles for therapeutic or imaging agents based on the pathological processes of atherosclerosis, with the ultimate goal of improving clinical symptoms. To achieve this, assembled nanoparticles must be efficiently delivered to specific tissues with cellular specificity and subcellular precision. Such effective and efficient nano-drug delivery requires complete control over nanoparticle transport in vivo; however, this level of control has not yet been achieved and represents a significant challenge in nano-platform development. To address this challenge, researchers need a better understanding of fundamental concepts regarding how nanoparticles interact with biological systems. Coating nanoparticle surfaces with polyethylene glycol (PEG) or "PEGylation" is a common method to improve drug and gene delivery efficiency to target cells and tissues. The systemic circulation time of PEG-coated nanoparticles can be modulated by altering PEG molecular weight, PEG surface density, and nanoparticle core properties [17]. Table 1 summarizes several nano-delivery platforms reported in recent years, covering aspects such as targets, particle size, and mouse models.

3.2 Membrane-Coated Biomimetic Nanoparticles

Existing research demonstrates that platelets and inflammatory cells participate in atherosclerotic plaque formation, a behavior exploited to develop platelet membrane-camouflaged nanoparticles that can deliver therapeutic drugs to atherosclerotic plaques. Yanan Song et al. developed a novel method using platelet membrane-coated nanoparticles (PNP) to mediate targeted rapamycin delivery for atherosclerosis treatment. They examined PNP targeting to atherosclerosis in vitro and in vivo, comparing the anti-atherosclerotic efficacy of rapamycin alone, rapamycin-loaded PNP (RAP-PNP), and PEGylated rapamycin nanoparticles (RAP-NP) [32]. PNP-targeted rapamycin delivery significantly enhanced its anti-atherosclerotic activity. RAP-PNP substantially

delayed atherosclerosis progression and stabilized plaques by reducing necrotic cores and macrophage numbers while increasing smooth muscle cell counts and collagen content.

Since the first report of membrane-coated biomimetic nanoparticles, numerous studies have explored their diagnostic and therapeutic potential. As mentioned, this biomimetic nanotechnology can prolong drug circulation time and endow nanoparticles with active targeting capabilities and inflammatory cytokine-neutralizing activity for cardiovascular disease treatment. However, infusing inappropriate cell membranes into the body can cause severe hemolytic reactions if fundamental understanding of complex cell membrane properties remains lacking. Therefore, prioritizing autologous cell membranes is essential. Moreover, research on membrane-coated nanoparticles remains at the laboratory stage, and enhanced safety assessments are needed to accelerate their clinical translation.

3.3 Peptide Amphiphile (PA) Supramolecular Nanostructures

Apolipoprotein A1 (ApoA1) is the primary protein component of high-density lipoprotein cholesterol and promotes cholesterol efflux from atherosclerotic plaques [33]. However, direct synthesis and incorporation of ApoA1 into therapeutics is unfeasible because it is a large, hydrophobic protein (21–31 kDa). Covalently binding an 18-amino-acid ApoA1-mimetic peptide (called "4F") to PA solves this problem. This peptide is approximately one-tenth the size of endogenous ApoA1, making it easier to synthesize and incorporate into nanomaterials while retaining ApoA1' s cholesterol efflux and binding functions in animals. Therefore, conjugating the 4F peptide to PA yields plaque-targeting nanocarriers, ApoA1 PA [34].

Chronic inflammation in atherosclerosis induces inflammatory cells and apoptotic vascular smooth muscle cells to release matrix metalloproteinases (MMPs), which degrade collagen and cause fibrous cap thinning and plaque destabilization [2]. The collagen cleavage site, recognized by the peptide sequence [VPMSMRGG] or Col-1 peptide, is identified by MMP-1 and undergoes rapid degradation. Deborah D. Chin et al. [35] incorporated the Col-1 peptide into peptide amphiphile micelle (PAM) nanoparticles and functionalized them with the C-C chemokine receptor-2 (CR2) binding motif of monocyte chemoattractant protein-1 (MCP-1) to target and treat unstable atherosclerotic plaques. For clinical relevance and adaptability, gadolinium decoration was added to the micelles to create monocyte-binding, collagenase-inhibiting, and gadolinium-modified peptide amphiphile micelles (MCG PAM) for simultaneous molecular magnetic resonance imaging of plaques. Through MRI, MCG PAM demonstrated enhanced targeting and successful plaque detection in diseased mice in vivo. Histologically, MCG PAM-treated mice showed 61% and 113% increases in fibrous cap thickness compared to non-targeted micelle- or PBS-treated mice, respectively, demonstrating MCG PAM' s potential for targeting, diagnosing, and treating

vulnerable plaques in atherosclerotic mice.

PA can be combined with various bioactive motifs to achieve diagnostic and therapeutic purposes. Based on these findings, future PA research directions will focus on developing integrated diagnostic-therapeutic targeting platforms.

3.4 Mesoporous Silica Nanoparticles (MSNs)

With rapid nanotechnology development, nanocarrier-based drug delivery systems have attracted widespread attention. Mesoporous silica has been widely used in nanodrug platform construction due to its advantages, including flexible size, large specific surface area, controllable pore volume, high drug loading capacity, good biocompatibility, hydrothermal stability, and chemically modifiable surfaces. Drug loading methods based on MSNs primarily include physical adsorption and solvent evaporation [36, 37]. The physical adsorption method involves soaking MSNs in drug-containing solutions until equilibrium is reached, with most drugs penetrating the carrier's pores. The solvent evaporation method combines physical adsorption with subsequent rapid solvent evaporation, offering faster drug dissolution than physical adsorption alone [38].

Pore morphology significantly affects drug loading and release. Wang et al. reported that MCM-48 with interconnected pore structures exhibited faster dissolution rates than MCM-41 with non-connected pore networks [39]. Additionally, SBA-16 with three-dimensional cage-like cubic mesoporous structures showed faster dissolution than MCM-41 with two-dimensional hexagonal arrangements because interconnected pore structures reduce diffusion barriers and facilitate drug diffusion into the dissolution medium [40]. Zhang et al. used three spherical MSNs with different pore sizes as carriers for TEL loading [41]. In vitro dissolution tests demonstrated that TEL dissolution rates increased with larger pore sizes.

Macrophages constitute the majority of cells in vulnerable plaques. For imaging assessment of high-risk plaques, particularly those with abundant macrophages, macrophages represent ideal targets. Menglin Wu et al. synthesized a novel magnetic mesoporous silica nanoparticle loaded with IR820 (PP1-IO@MS-IR820, PIMI) [42]. Iron oxide (IO) served as the magnetic core for T2- and T2-weighted magnetic resonance imaging, while mesoporous silica loaded with the NIRF dye (IR820) enabled optical imaging. Superimposing these two imaging components achieved dual-modal imaging effects.

Although these studies demonstrate MSN effectiveness in animal models, the key to ultimate clinical translation lies in proving long-term MSN safety, testing different administration routes, and enabling scalable production for commercial synthesis reproducibility.

3.5 DNA/RNA-Based Nanostructures

Recent studies have reported glycan-based nanomaterials, such as hyaluronic acid-based NPs [43] and glycan amphiphilic NPs [44], for targeting atherosclerotic plaques and inhibiting macrophage proliferation. Developing nanoparticle platforms targeting plaques based on nucleic acids also represents a novel direction. Lei Zhang et al. developed DNA-coated superparamagnetic iron oxide nanoparticles (DNA-SPIONs) [7] that effectively target plaques. The designers proposed that DNA oligonucleotides as NP shells confer negative surface charges [45], thereby promoting macrophage uptake.

Reactive oxygen species (ROS) are intracellular free radicals composed of OH^-, H_2O_2, O_2^-, etc. ROS levels in macrophages within atherosclerotic plaques are higher than in normal cells, closely correlating with AS development and progression [46]. Based on these findings, JM Li et al. [47] used an amino acid-based nanoparticle carrier, HB-OLD7, to locally deliver NOX2-targeting siRNA to arterial walls. This approach reduced arterial wall Cybb gene expression by 48.7%, decreased neointima/media area ratios by 48.3%, and increased lumen/total arterial area ratios by 48.9%.

DNA/RNA-based nanomaterials exhibit excellent selective targeting and represent safe, efficient, specific, and non-pathogenic gene therapy materials. Combining gene therapy with nano-delivery systems broadens the therapeutic and biomedical applications of these molecules. The delivery system is critical for nucleic acid drug efficacy, as nucleic acids are negatively charged biological macromolecules that struggle to cross cell membrane phospholipid bilayers. Additionally, delivered DNA/RNA is susceptible to degradation by nucleases in the body, representing technical barriers to clinical translation.

3.6 Application of Metal Nanoparticles

Metal nanoparticles play increasingly important roles in atherosclerosis diagnosis, treatment, and prevention due to their unique advantages. Sudden rupture of vulnerable plaques formed during atherosclerosis triggers cardiovascular events, and plaque vulnerability closely correlates with plaque composition. Macrophages are the most abundant cellular component in vulnerable plaques, constituting over 80% of plaque content [48]. A key early feature of atherosclerosis is the overexpression of class A scavenger receptors (SR-A) on surfaces that activate macrophages to phagocytose oxidatively modified low-density lipoprotein (oxLDL), forming foam cells. Man Ye et al. successfully prepared SR-A-targeted metal nanoparticles, Fe-PFH-PLGA/CS-DS nanoparticles, and characterized their properties [4]. Subsequent targeting tests demonstrated that Fe-PFHPLGA/CS-DS nanoparticles selectively accumulated in activated macrophages within aortic plaques and induced apoptosis in cultured rat aortic plaque cells upon low-intensity focused ultrasound irradiation. Christopher Poon et al. reported hybrid metal oxide-peptide amphiphile micelles (HMO-ms) [49] that combine inorganic, magnetic iron oxide or manganese oxide cores with

organic, fibrin-targeting peptide amphiphiles composed of CREKA sequences for potential atherosclerotic plaque targeting.

Compared with conventional sensitive modified materials, metal nanoparticles are extremely small (1-100 nm in diameter). The surface effects of nanomaterials give metal nanoparticle-modified materials large specific surface areas and substantial effective contact areas with reactants, enhancing in vivo drug transport efficiency. However, enhanced in vivo toxicological assessments are required before clinical translation.

4. Application of Exosome-Targeted Drug Delivery Systems in Atherosclerosis

Exosomes are small, single-membrane secretory organelles approximately 30-200 nm in diameter with the same topology as cells, enriched with selected proteins, lipids, nucleic acids, and glycoconjugates. As extracellular vesicles, exosomes play important roles in intercellular signaling and communication, immune response, cellular homeostasis, autophagy, and infectious diseases [50]. With deeper research into extracellular vesicles and atherosclerosis, exosomes have been employed as targeted drug delivery strategies for treating atherosclerosis [51]. Compared with artificially synthesized nanotechnology drug delivery systems, exosomes as naturally derived drug delivery carriers exhibit better biodistribution, biodegradability, immunocompatibility, and reduced toxicity.

Exosome drug loading methods typically depend on the drug type. Small molecules are usually loaded through passive incubation or active loading methods that purposefully disrupt exosome membrane integrity to enable drug loading. Active loading methods are often preferred over passive methods due to higher efficiency, including electroporation, sonication, and liposome insertion techniques [52].

An in vitro study confirmed the potential of endothelial-derived exosomes to deliver siRNA to primary endothelial cells isolated from mouse aorta [53], suggesting that exosomes may serve as a natural drug delivery system for transporting therapeutic nucleic acids to inflamed endothelium in atherosclerosis. The nucleic acids miR-143/145 found in exosomes can prevent smooth muscle cell dedifferentiation; intravenous injection of exosomes enriched with these miRNAs into high-fat diet-fed $ApoE^{-}/^{-}$ mice reduced aortic fatty lesions by approximately twofold and prevented atherosclerotic lesion formation [54]. Wu et al. loaded the small-molecule therapeutic hexyl 5-aminolevulinate hydrochloride (HAL) into M2 macrophage-derived exosomes via electroporation [55]. After treating macrophages with drug-loaded exosomes, IL-6 and TNFα expression decreased significantly. Moreover, stronger localization of drug-loaded exosomes in atherosclerotic plaques was observed in $ApoE^{-}/^{-}$ mice compared to free HAL, and drug-loaded exosomes substantially reduced plaque area. These studies demonstrate that enriching exosomes with therapeutic miRNAs through genetic approaches enables effective atherosclerosis treatment.

Exosome drug loading is likely to become the next-generation drug delivery mechanism, combining nanoparticle dimensions with non-cytotoxic effects, high drug loading capacity, and low immunogenicity.

5. Challenges

While industrial nanodrugs have gained widespread attention for targeted cardiovascular disease diagnosis and treatment in recent years, several issues have emerged. In the human body, nanodrugs are typically recognized as threats by the innate immune system, leading to unwanted clearance due to complement activation. When nanoparticles are injected intravenously, large amounts of complement protein C3b bind to nanoparticle surfaces, potentially causing uncontrolled complement system activation that endangers life [56, 57]. Such adverse reactions have been reported in studies of liposomal nanformulations like Doxil [58] and inorganic nanoparticles such as iron oxide and metal nanoparticles [59, 60].

Over the past decade, nanodrug targeting strategies have experienced unprecedented growth, while these adverse reactions and toxic side effects reflect challenges that must be overcome for broader nano-delivery platform implementation. Although most nanodrug preclinical studies have been successful, batch production and application remain challenging, requiring extensive clinical trials to substantiate their safety. Unlike industrial nano-targeting platforms, exosome drug-loading platforms offer better biocompatibility and lower immunogenicity; however, imperfect extraction procedures and poor reproducibility represent major challenges [61].

6. Summary and Outlook

This review highlights recent research progress on nanocarrier particles and exosomes for targeted diagnosis and treatment of atherosclerosis. In recent years, research and applications of nano-delivery platforms in targeted imaging and atherosclerosis therapy have continuously increased. These targeted delivery systems differ from conventional administration methods, offering significant advantages in controllability and targeting that enable targeted drug delivery to lesion sites, thereby reducing drug toxic side effects to some extent. This results from controlled drug release and improved pharmacokinetics and pharmacodynamics. While the effectiveness of nanoparticle drug delivery systems has been largely proven experimentally, clinical translation remains a major challenge due to issues with biocompatibility, circulation half-life, and drug retention in vivo. Future efforts must focus on improving targeting precision and reducing side effects.

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for feasibility analysis; Xu Shangfu for quality control and final approval, with overall responsibility and supervision.

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Note: Figure translations are in progress. See original paper for figures.