International Journal of Nanomedicine

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REVIEW

Macrophage-Targeted Nanomedicine for the Treatment of Atherosclerosis

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Abstract: Cardiovascular and cerebrovascular diseases are the leading causes of mortality worldwide, with atherosclerosis being the primary etiology. Despite its prevalence, atherosclerosis remains inadequately controlled by conventional therapeutic interventions. The unique physicochemical properties of nanomedicine offer new hope for the treatment of atherosclerosis. Macrophages are now understood to play a pivotal role in the progression of atherosclerosis, acting as both pathogenic factors and potential therapeutic targets. The inherent plasticity of macrophages significantly influences disease progression, suggesting that modulating macrophage function or abundance could provide a viable strategy to intervene in the atherosclerotic process. This review comprehensively examines the targeted delivery and controlled release of nanoparticles, providing an in-depth analysis of both passive and active targeting strategies, as well as the controlled release of therapeutic agents in response to the specific microenvironment of atherosclerotic plaques and external stimuli such as light and sound. The role of biomimetic nanomedicines in the treatment of atherosclerosis, primarily those utilizing macrophage membrane coatings and exosomes, is discussed. Finally, the current challenges facing nanomedicine in atherosclerosis treatment are analyzed, emphasizing the need for future research to investigate its mechanisms of action in depth and optimize related strategies to harness its therapeutic potential.

Keywords: nanomedicine, macrophage, atherosclerosis, targeted delivery, responsive strategies

Introduction

Atherosclerosis (AS) is a chronic and progressive disease[1] characterized by subtle changes in the vascular walls that often precede the onset of organ damage due to vascular narrowing.[2] In recent years, shifts in the demographic patterns of AS have been observed, notably a decrease in the age of onset and an increase in the prevalence among women.[3]

Statins, widely recognized for their potent lipid-lowering efficacy, remain the cornerstone of AS management in both primary and secondary cardiovascular prevention. Robust clinical research[4,5] underscores their ability to stabilize plaques and reduce cardiovascular events by modulating lipid profiles. However, their therapeutic utility is constrained by dose-dependent adverse effects, including hepatotoxicity and myopathy,[6] which necessitate periodic monitoring of hepatic enzymes and creatine kinase levels. In recent years, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors have emerged as a transformative adjunctive therapy, demonstrating unparalleled efficacy in lowering low-density lipoprotein cholesterol (LDL-C) levels through targeted degradation of hepatic LDL receptors.[7,8] Despite their significant promise, logistical challenges such as high costs and the need for subcutaneous administration currently limit their accessibility in routine clinical practice.[9] Therapeutic strategies for advanced AS complications, notably thrombotic events, incorporate antiplatelet agents (eg, aspirin) to mitigate platelet aggregation. Long-term antiplatelet regimens,

Received: 8 April 2025
Accepted: 16 July 2025
Published: 25 August 2025

while effective in secondary prevention, carry an elevated risk of hemorrhagic complications,[10,11] underscoring the need for risk stratification during patient selection.

In recent years, the application of nanotechnology in treating various diseases has grown exponentially.[12,13] Compared with traditional drug formulations, nanomedicines can achieve precise localization and targeted delivery to lesion sites by modifying specific targeting molecules, such as antibodies and peptides.[14] Furthermore, nanotechnology can potentially enhance drug solubility, stability, and bioavailability.[15] Nanomedicines also enable responsive drug release,[16] enhancing therapeutic efficacy and reducing side effects associated with premature release. As research continues to deepen our understanding of the pathophysiological mechanisms of macrophages in AS and as nanotechnology undergoes ongoing innovation, nanomedicines are expected to play a more significant role in the treatment of AS, providing new strategies and methods for the prevention and treatment of cardiovascular and cerebrovascular diseases.

In this review, we explore advancements in research on macrophage-targeted nanomedicines for the treatment of AS. The dual role and plasticity of macrophages in AS are initially examined. Subsequently, methodologies for targeting plaque macrophages with nanodrugs are investigated, and strategies for achieving controlled drug release through the manipulation of internal or external environmental cues are discussed. Moreover, the latest developments in the application of macrophage-associated biomimetic nanodrugs for the management of AS are reviewed. Finally, the challenges faced by nanomedicines in the clinical translation of AS treatment are analyzed, and a perspective on their future development is provided.

Dual Role of Macrophages in Atherosclerosis

Revisiting Macrophages: Pathogenic Agents and Therapeutic Targets

The pathological hallmark of AS is the accumulation of lipids and abnormal inflammatory responses within the arterial wall, with macrophages playing a crucial role in the development of AS and the formation of foam cells, which constitute more than 80% of the cellular components of plaques.[17] During the initial stages of AS, hyperlipidemia or long-term hypertension leads to endothelial cell damage,[18] allowing apolipoprotein B-containing lipoproteins (ApoB-LPs), such as LDL, to enter the arterial intima. Under the influence of proteoglycans, LDL is oxidized to form ox-LDL, which accumulates beneath the endothelium.[19] Oxidized LDL (Ox-LDL) is a key trigger for early inflammatory responses. It activates the overlying endothelial cells, prompting them to secrete chemokines that recruit monocytes from the bloodstream into the subintimal layer.[20] Monocytes differentiate into macrophages under the influence of macrophage-colony stimulating factor (M-CSF), with the upregulation of scavenger receptor A1 (SR-A1) and CD-36,[21] enabling them to recognize and internalize ox-LDL. The engulfment of ox-LDL transforms macrophages into foam cells, which are laden with lipids.[22] Foam cells, in turn, secrete various cytokines and inflammatory mediators, including tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6).[23] These molecules stimulate the upregulation of adhesion molecules on endothelial cells, such as intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1). VCAM-1 can be recognized by integrins α4 and β1 on the macrophage membrane, thereby recruiting more macrophages into the inflammatory area.[24] These macrophages then transform into foam cells, creating a vicious cycle that intensifies the inflammatory response and the progression of atherosclerotic lesions.

In advanced lesions, macrophages may undergo apoptosis through various mechanisms, including growth factor deprivation,[19] oxidative stress, and endoplasmic reticulum stress.[25] Furthermore, due to impairments in phagocytic clearance mechanisms,[26] apoptotic macrophages are not effectively removed, leading to the accumulation of cellular debris and lipids within the plaque and the formation of a necrotic core. The formation of a necrotic core further exacerbates the inflammatory response and increases the risk of plaque rupture. Moreover, macrophages secrete substances such as matrix metalloproteinases (MMPs),[27] which degrade the extracellular matrix, thereby compromising the structural integrity of the fibrous cap and increasing the plaque more susceptibility to rupture. Upon plaque rupture, the exposure of subendothelial components activates the coagulation system, leading to platelet aggregation and thrombus formation, triggering acute cardiovascular and cerebrovascular events.

In summary, macrophages are significant pathogenic factors contributing to the progression of AS and are highly promising targets for disease treatment. Future in-depth research into the complex mechanisms of macrophages in AS is

expected to yield more innovative and effective therapeutic strategies. These advancements have the potential to offer new hope for patients with AS and to drive significant advancements in AS treatment.

Plasticity of Macrophages and Their Transformation in the Progression of Atherosclerosis

Macrophages exhibit a high degree of plasticity, enabling them to adopt diverse phenotypic characteristics under various microenvironmental stimuli. Classically activated macrophages (M1) and alternatively activated macrophages (M2) are the two most common phenotypes of macrophages. M1 macrophages, which are typically induced by cytokines such as lipopolysaccharide (LPS) and interferon-γ (IFN-γ),[28] activate key signaling pathways, including nuclear factor-κB (NF-κB) and STAT1 (signal transducer and activator of transcription 1). This activation leads to the secretion of substantial quantities of inflammatory mediators, including IL-1β, IL-6, reactive oxygen species (ROS), and nitric oxide (NO).[29] These mediators play critical roles in driving inflammatory responses, recruiting additional immune cells to the injury site, and contributing to the expansion of plaque volume. Consequently, the fibrous cap becomes thinner, plaque stability is significantly compromised, and the risk of acute cardiovascular and cerebrovascular events is markedly elevated.

In contrast, under the influence of anti-inflammatory cytokines such as IL-4 and IL-13,[30] certain macrophages polarize toward the M2 phenotype. M2 macrophages highly express IL-10 while downregulating IL-12 and IL-23.[31] These cells primarily focus on anti-inflammatory functions, suppress inflammatory cascades, and participate in tissue repair and vascular regeneration. By stabilizing plaque structure and improving the local vascular environment, M2 macrophages offer a potential therapeutic opportunity for alleviating AS lesions. Studies have shown that M1 macrophages are predominantly found in late-stage unstable plaques, whereas M2 macrophages are more highly expressed in stable plaque regions,[32] indicating that the balance between M1 and M2 macrophages is closely related to plaque outcomes. Therefore, promoting the polarization of M1 to M2 macrophages has become a promising strategy for treating AS.

In addition, various intermediate phenotypes and unique subtypes of macrophages are present within plaques, such as the Mox macrophage population, M(Hb) and Mhem populations, M4 macrophages, and IL-17A-stimulated macrophages.[33] Among these, Mox macrophages, which are induced by oxidized phospholipids, are widely distributed in plaques and account for 30% of plaque macrophages.[34] The role of Mox macrophages in AS has yet to be fully explored. Zhai et al reported that nanoparticles (NPs) with intermediate hydrophobicity (C4NP) could induce macrophage polarization toward the Mox phenotype by activating the Nrf2 and HO-1 signaling pathways,[35] which helps to further understand the complex role of macrophages in the occurrence and development of AS and provides new clues for exploring the pathogenesis of AS (Figure 1).

Macrophage-Targeted Nanomedicines

Nanocarrier Platforms: Classification and Design Principles

The efficacy of macrophage-targeted nanomedicines heavily relies on the rational design of nanocarrier platforms. Based on material composition and functional mechanisms, current nanocarriers can be categorized into four major classes (Table 1). The structure of the nanomedicine delivery system is illustrated in Figure 2.

Organic Nanocarriers

Lipid-Based Nanoparticles (LNPs)

Lipid-based nanoparticles (LNPs), encompassing liposomes and solid lipid nanoparticles (SLNs), are structurally characterized by spherical vesicles formed from a phospholipid bilayer (liposomes) or a solid lipid core (SLNs).[36] To enhance macrophage-specific targeting, these nanoparticles are often surface-functionalized with ligands such as mannose[37] or CD36 antibodies,[38] which facilitate receptor-mediated uptake via scavenger receptors (eg, SR-A1 or CD36) expressed on macrophages. Liposomes, for instance, can be loaded with docosahexaenoic acid, a bioactive lipid that polarizes macrophages toward the anti-inflammatory M2 phenotype,[39] thereby reducing plaque inflammation and promoting cholesterol efflux from foam cells. SLNs, on the other hand, excel in encapsulating hydrophobic therapeutics, such as simvastatin,[40] enabling sustained drug release within the plaque microenvironment to inhibit macrophage-driven necrotic core expansion.

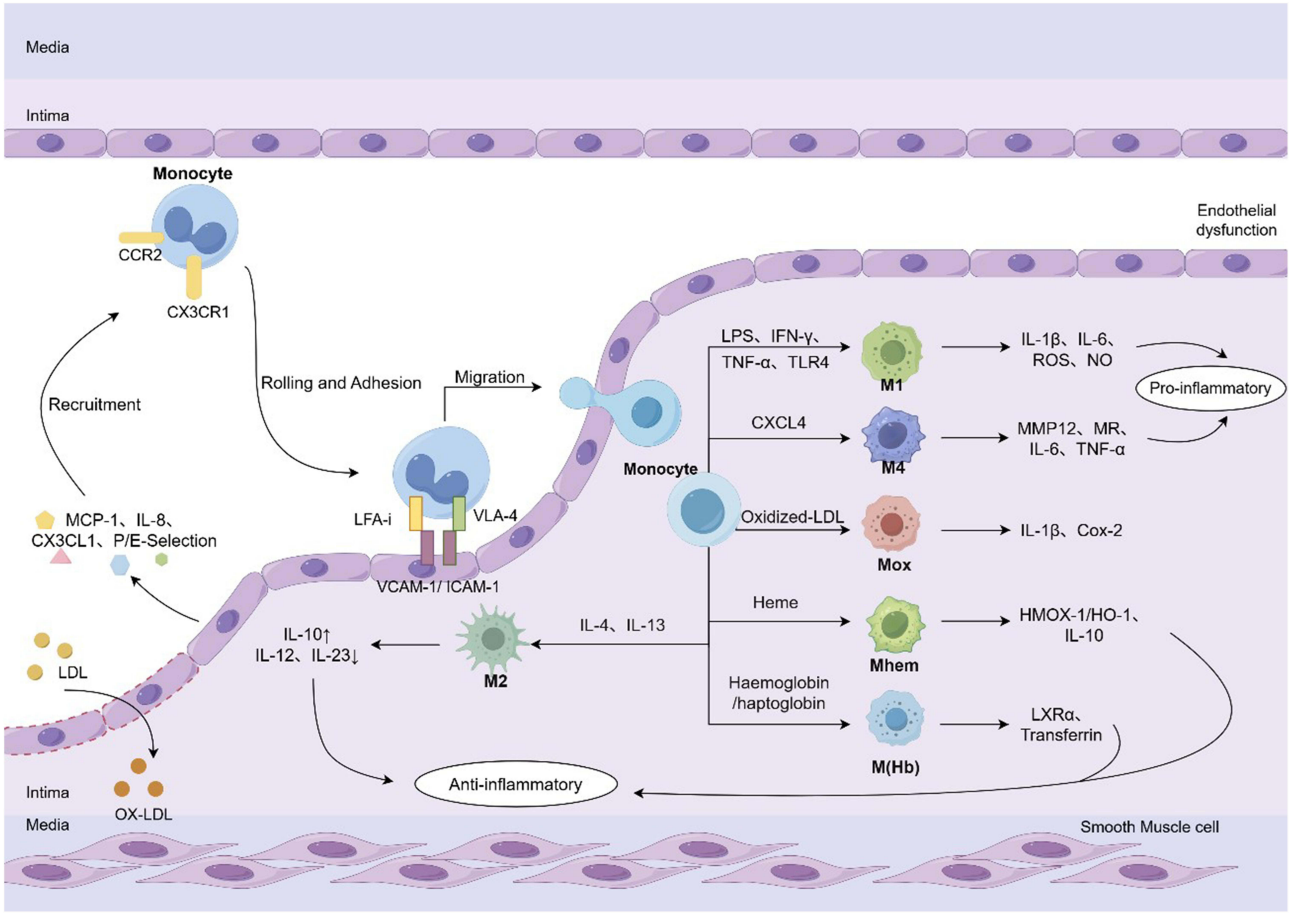

Figure 1 Macrophage Polarization Phenotypes and Their Roles in AS. During the development and progression of atherosclerosis, the recruitment, adhesion, and migration of monocytes, as well as the different phenotypes of macrophage polarization. Created by Figdraw.

Polymeric Micelles

Polymeric micelles, self-assembled from amphiphilic block copolymers like poly(lactic-co-glycolic acid) (PLGA) and polyethylene glycol (PEG), form a hydrophobic core (for drug encapsulation) and hydrophilic shell that enhances

Table 1 Comparative Analysis of Nanocarrier Platforms for Atherosclerosis Therapy

Category	Subtypes	Advantages	Disadvantages
Organic Nanocarriers	LNPs, Polymeric micelles, Dendrimers	High biocompatibility and biodegradability; Tunable drug-loading capacity; Stimuli-responsive drug release; Scalable production	Rapid clearance by the MPS; Low drug-loading efficiency for micelles; Dendrimer cytotoxicity at high doses
Inorganic Nanocarriers	MSNs, AuNPs, SPIONs	High surface area and pore volume; Multimodal theranostics; Magnetic targeting (SPIONs); Photothermal capabilities (AuNPs)	Limited biodegradability; Potential oxidative stress (SPIONs); High cost (AuNPs); Rapid clearance for small MSNs
Biomimetic Nanocarriers	Cell membrane-coated NPs, rHDL, Exosomes	Natural targeting via inherited receptors; Immune evasion and prolonged circulation; Dual therapy	Batch-to-batch variability in membrane integrity, Low exosome yield and scalability challenges, Rapid renal clearance (rHDL)
Hybrid Systems	MLP-NVs, Stimuli-responsive nanogels	Synergistic multifunctionality; Enhanced penetration into dense plaques; Spatiotemporal control	Complex fabrication processes; Potential immunogenicity from hybrid components; Limited mechanical stability (nanogels)

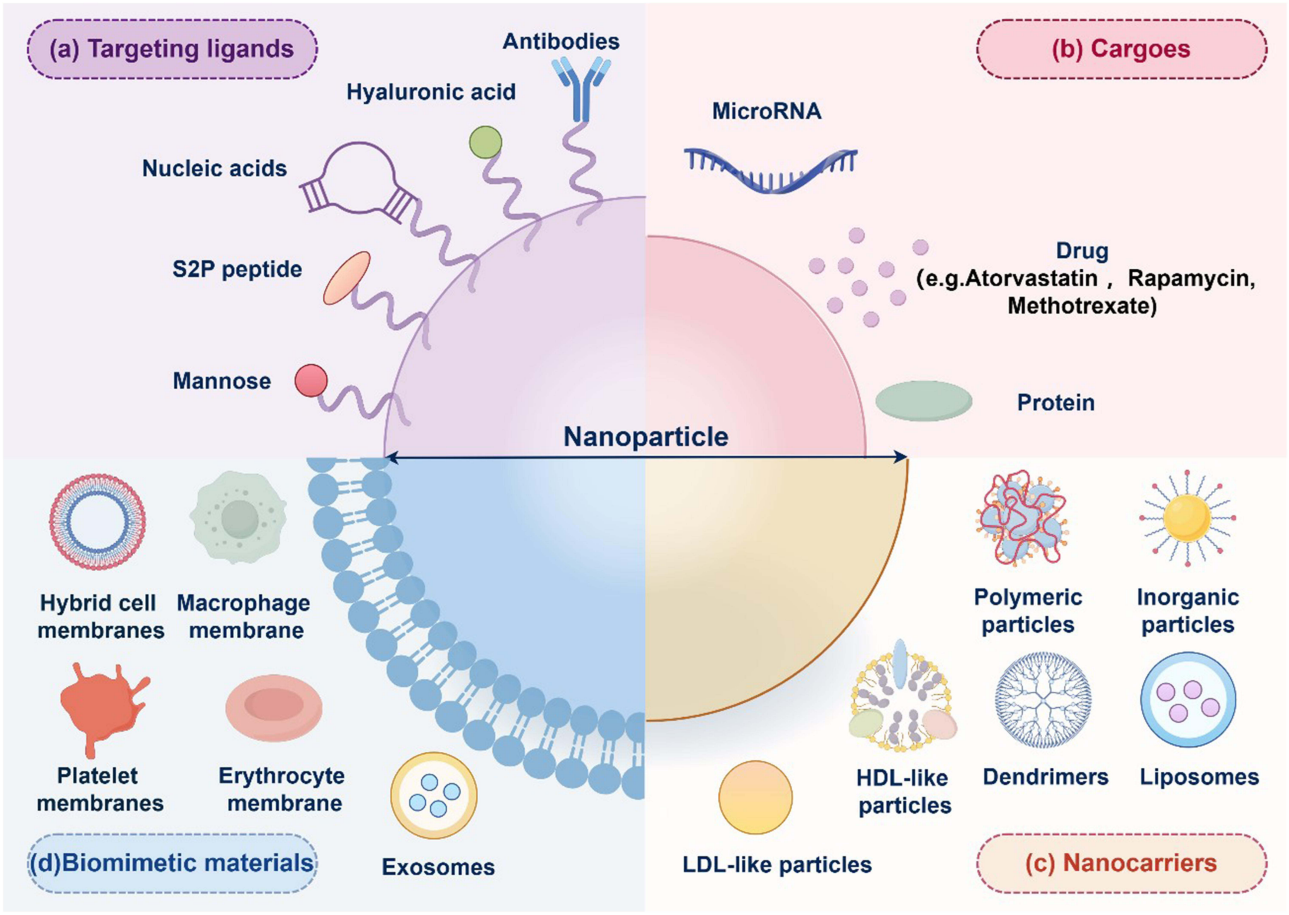

Figure 2 Schematic representation of the drug delivery nanosystem. (**a**) Targeting macrophage-specific ligands. (**b**) Cargoes exerting therapeutic effects. (**c**) Nanomaterials commonly used for the treatment of atherosclerosis. (**d**) The types of biomimetic nanomaterials currently in use. Created by Figdraw.

stability and prolongs circulation by minimizing opsonization and renal clearance. To target macrophages, micelles are functionalized with hyaluronic acid (HA), which binds CD44 receptors on pro-inflammatory macrophages in plaques. HA-PLGA micelles co-deliver anti-inflammatory agents (eg, rapamycin) and ROS scavengers (eg, SOD mimetics), synergistically reducing oxidative stress and stabilizing plaques. Their stimuli-responsive design—activated by plaque-specific acidic pH or ROS[41]—enables controlled drug release at the lesion site, minimizing systemic toxicity.

Dendrimers

Dendrimers are hyperbranched, monodisperse polymers with precise radial architecture and surface functionality. Kou et al demonstrated that polyamidoamine (PAMAM) dendrimers exhibit a hollow architecture and surface amine groups modifiable with PEG-mannose, enabling macrophage-specific targeting via mannose receptors. By employing flash nanoprecipitation with a custom multi-inlet vortex mixer, scalable synthesis (9.6 L/h) of cross-linked NPs was achieved with unprecedented drug-loading capacity (37%) and encapsulation efficiency (76%). The PEGylation reduced surface charge (+17.3 mV to +4.1 mV), minimizing cytotoxicity in RAW 264.7 macrophages and HUVECs.[42]

Inorganic Nanocarriers

Mesoporous Silica Nanoparticles (MSNs)

MSNs are characterized by a high-surface-area silica framework with radially ordered mesopores, enabling efficient encapsulation of therapeutic agents.[43] These nanoparticles are functionalized with stimuli-responsive linkers, such as thioketal bonds, to achieve ROS-triggered drug release within atherosclerotic plaques.[44] Their engineered near-infrared fluorescence properties (eg, via ICG loading) further support real-time tracking of drug delivery dynamics.[45]

https://doi.org/10.2147/IJN.S529988

Gold Nanoparticles (AuNPs)

Gold nanoparticles, featuring tunable surface plasmon resonance properties, adopt either spherical or rod-shaped morphologies to optimize light-to-heat conversion efficiency. Under near-infrared irradiation, AuNPs generate localized hyperthermia, inducing photothermal ablation[46] of pro-inflammatory macrophages and reducing necrotic core expansion. Concurrently, their strong photoacoustic signals enable high-resolution imaging of plaque morphology.[47]

Superparamagnetic Iron Oxide Nanoparticles (SPIONs)

SPIONs consist of iron oxide cores coated with dextran or PEG, which ensures colloidal stability and reduces immunogenicity. Functionalization with anti-CCR2 antibodies facilitates targeted binding to inflammatory monocytes expressing CCR2 receptors, thereby directing nanoparticles to the atherosclerotic lesions.[48] Magnetic guidance further improves their accumulation in plaque microenvironments.

Biomimetic Nanocarriers

Cell Membrane-Coated Nanoparticles (CMC@NPs)

CMC@NPs are synthesized via extrusion, ultrasonication, or microfluidics, balancing yield, stability, and scalability. These membranes include red blood cells (RBCs), which confer immune evasion via CD47-mediated "don't eat me" signals to prolong circulation (>72 h);[49] leukocytes (eg, neutrophils, macrophages) that inherit chemotactic receptors (CCR2, CXCR4) for active homing to inflammatory or tumor sites;[50] platelets rich in adhesion molecules (P-selectin) for targeting injured vasculature;[51] cancer cell membranes enabling homotypic tumor targeting via surface biomarkers;[52] stem cell membranes with inherent tropism for diseased tissues;[53] bacterial outer membranes carrying pathogen-associated molecular patterns for immune modulation;[54] and hybrid membranes (eg, RBC-platelet fusions[55]) that integrate multifunctional properties. The membrane coating strategy offers inherent advantages, including immune evasion, ligand-receptor-driven targeting, enhanced biocompatibility, and protection of encapsulated payloads from enzymatic degradation.

Reconstituted High-Density Lipoprotein (rHDL)

rHDL nanoparticles are engineered by complexing apoA-I mimetic peptides with phospholipids,[56] forming discoidal or spherical nanostructures that mimic endogenous HDL. rHDL can be functionalized with hydrophobic drugs (eg, statins[57]) to achieve dual therapeutic effects: promoting cholesterol efflux via ATP-binding cassette transporter A1 (ABCA1) and suppressing plaque inflammation.[57]

Exosome-Based Therapeutic Systems

Exosomes, natural extracellular vesicles (30–150 nm) secreted by stem cells or macrophages,[58] are typically engineered to deliver immunomodulatory cargo (eg, anti-miR-155,[59] IL-10 mRNA[60]) for cardiovascular therapy. Macrophage-derived exosomes polarize pro-inflammatory M1 macrophages toward anti-inflammatory M2 phenotypes via miRNA transfer, stabilizing atherosclerotic plaques in preclinical models.[61] Their innate biocompatibility, low immunogenicity, and ability to cross biological barriers make them superior to synthetic carriers for sustained drug delivery. However, challenges include low yield during ultracentrifugation-based isolation, variability in cargo loading, and insufficient targeting precision.[58]

Emerging Hybrid Systems

Emerging hybrid nanosystems represent a transformative approach in cardiovascular therapeutics, particularly for AS, by synergistically integrating organic, inorganic, and biomimetic components to address multifactorial disease mechanisms. Macrophage-lipoprotein hybrid nanovesicles (MLP-NVs), engineered by fusing anti-inflammatory M2 macrophage membranes with lipidated peptides,[62] demonstrate dual functionality: they suppress inflammation and enhance cholesterol efflux. Other hybrid platforms, such as shear-responsive nanogels[63] and phototherapeutic nanosystems, further illustrate the versatility of this approach. Collectively, these hybrid systems overcome traditional limitations, such as poor targeting and systemic toxicity, by combining biomimetic tropism, microenvironment-responsive drug release, and multifunctional synergy, positioning them as promising candidates for precision medicine in cardiovascular diseases.

Passive Targeting

The design of nanomedicines necessitates not only precise targeting specificity to the diseased site but also stability within the physiological environment. Figure 3 illustrates the systemic uptake, plaque accumulation, and therapeutic action of nanomedicine.

Leveraging the intrinsic properties of these nanocarriers, passive targeting strategies exploit macrophage phagocytosis[64] and pathological enhanced permeability and retention (EPR) effects to localize therapeutics within plaques.[65,66] These NPs are subsequently internalized by macrophages via non-specific phagocytosis, with the majority being transported to lysosomes for degradation or further processing (Table 2).

The selection of nanomaterials plays a crucial role in the treatment of AS. Among the commonly used nanomaterials are polymeric nanomaterials, metallic nanomaterials, liposomes, dendrimers, and biological nanomaterials. Notably, the US Food and Drug Administration (FDA) has approved two polymeric materials, PLA and PLGA, for their extensive application in creating degradable high-molecular-weight nano-drug carriers.[83] Giacalone et al encapsulated RSG in PLA-PEG NPs to evaluate its uptake by RAW264.7 cells compared with that of free radiolabeled rosiglitazone (RSG).

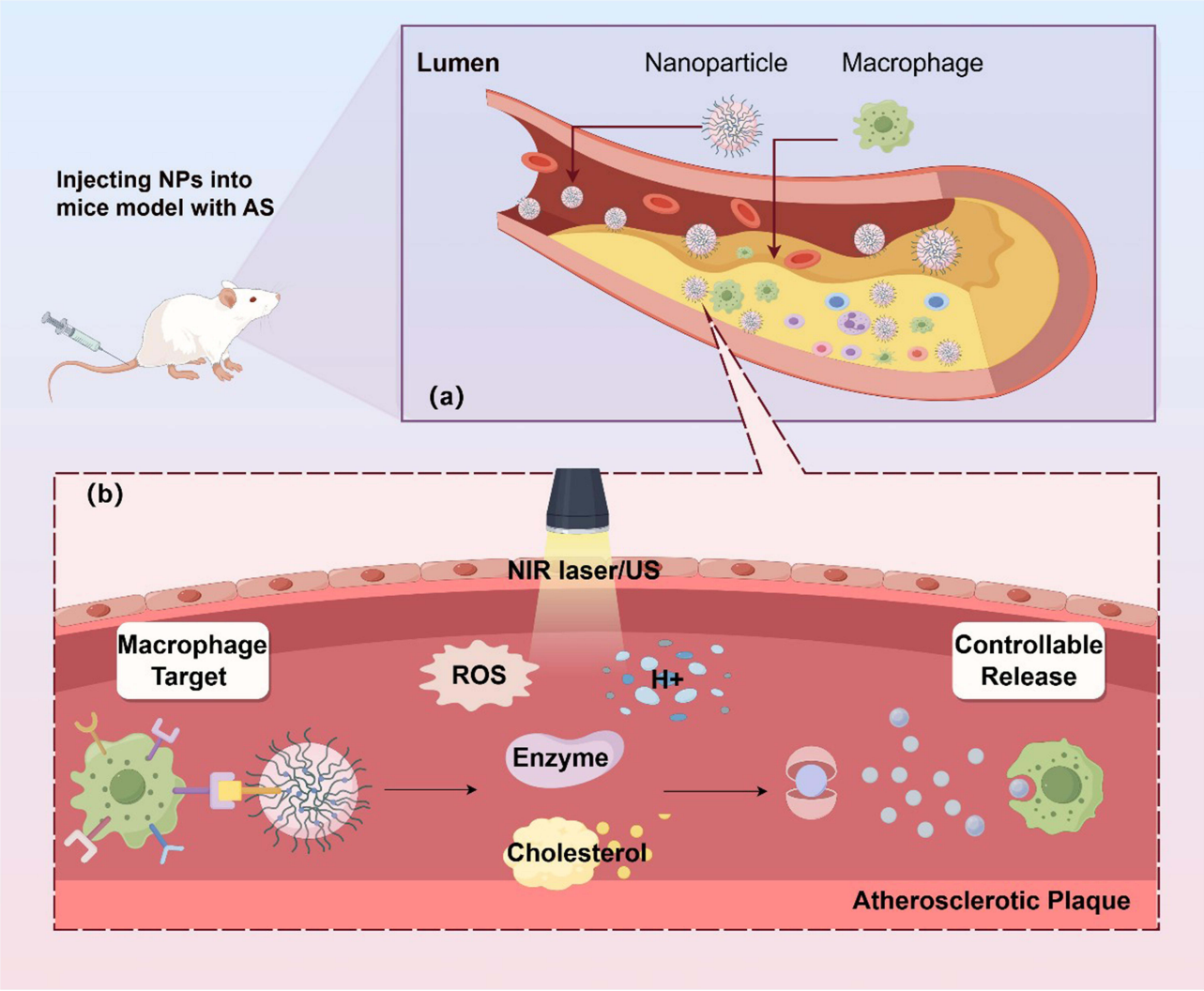

Figure 3 Journey of nanomedicines to macrophages. (**a**) Due to increased vascular permeability, nanomedicines accumulate at atherosclerotic plaque sites. (**b**) After entering the plaque area, macrophages recognize and phagocytose nanomedicines through passive or active targeting. Under the stimulation of the plaque microenvironment or external environments, such as laser and ultrasound, they release the loaded drugs, acting on macrophages to exert therapeutic effects on atherosclerosis. Created by Figdraw.

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Table 2 Passive Targeting of Macrophages for the Treatment of Atherosclerosis

Nanoparticle Platform	Cargo(es)	Cell and(or) Mouse Model	Effects	Ref.
PLGA	Curcumin and Bioperine	THP-1	Downregulate pro-inflammatory pathways and scavenger receptors involved in cholesterol uptake; inhibit the formation of foam cells	[67]
AgNPs	Oligonucleotide CpG	ApoE-/- mouse model with AS; BMDMs	Enhance efferocytosis; antioxidative and anti-inflammatory activities to promote the M1-to-M2 phenotypic switch of macrophages.	[68]
Carrier-free	TA and IR820 labeling	RAW 264.7; ApoE-/- mouse model with AS	Scavenge ROS, reduce inflammatory responses and promote M2 polarization of macrophages.	[32]
PEG-PLA/PLGA-based nanoparticles	PIO	THP-1	By activating PPAR-γ, PIO reduces the expression of pro-inflammatory cytokines.	[69]
Black phosphorus quantum dots (BPQDs)		ApoE-/- mouse model with AS	Promote autophagy in macrophages to regulate intracellular lipid metabolism and reduce lipid accumulation.	[70]
Carrier-free	Indole molecules and PB	Raw264.7; Male C57BL/6 mice	Eliminate ROS, decrease the expression of inflammatory cytokines, and achieve FL imaging	[71]
Tetrapod needle-like Pd-H (TN-PdH) nanozyme		RAW 264.7; ApoE-/- mouse model with AS	ROS scavenging, hydrogen anti-inflammation, and autophagy activation.	[72]
LPs	XMOTIF-tagged anti-miR-33a-5p	Immortalized Mouse Aortic Endothelial Cells(iMAECs) and RAW 264.7	Increase apoAI-mediated cholesterol efflux via ABCA1 upregulation.	[73]
PLA and/or PLGA.		RAW 264.7; BMDMs; ApoE-/- mouse model with AS	Enhance lysosomal degradation, promote macroautophagy/autophagy and protein aggregate removal, reduce apoptosis and inflammasome activation.	[74]
MSN	Necrosulfonamide (NSA)	RAW264.7;BMDM; MDM	Inhibit the formation of GSDMD pores, prevent the release of IL-1β, and suppress inflammatory responses.	[75]
Phospholipid-based, HDL-like nanoparticle		J774A.1 Cells;THP-1 Derived Macrophages;HEK-Blue-hTLR4 Cells;ApoE-/- mice and Ldlr-/- mice were fed on a western diet	Cholesterol crystal dissolution; enhance cholesterol efflux; anti-inflammatory effects; plaque stabilization.	[76]
Porous manganese-substituted Prussian blue (PMPB) nanocubes	Simvastatin	RAW 264.7; ApoE-/- mouse model with AS	Scavenge ROS and mitigate inflammation.	[77]
Spherical polymeric nanoparticles/liposomes	Methotrexate	RAW 264.7; BMDMs; ApoE-/- mouse model with AS	Halt monocytes' maturation and recruitment; modulation of lipoprotein transport; anti-inflammatory activity.	[78]
PLGA	Pitavastatin	THP-1;ApoE-/- mouse model with AS	Regulate lipid metabolism, and inhibit the secretion of inflammatory markers.	[79]
Chitosan nanoparticles	miRNA-33 mimics	BMDM; PM; C57BL6	Regulate ABCA1 expression and cholesterol efflux.	[80]
PLA	Rosiglitazone	RAW264.7	Improve the anti-inflammatory effect	[81]
HDL-like nanoparticles	A lipophilic small molecule inhibitor (SMI 6877002)	ApoE-/- mouse model with AS	Reduce monocyte recruitment; inhibition of proinflammatory signaling.	[82]

These findings revealed that nanoparticle-mediated RSG uptake was markedly greater than that of free RSG.[81] Similarly, Sun et al utilized PLGA to encapsulate pitavastatin (P-NP) and reported that, in ApoE$^{-/-}$ mice with AS, the P-NP group presented a significantly lower plaque area (15.7±1.08%) than did the intravenous (26.9±1.55%) and oral (17.3±0.56%) pitavastatin groups.[79] These results substantiate the efficacy of employing nanomaterials as drug delivery vehicles, which can increase drug concentrations within the pathological region, extend the therapeutic duration of the medication, and thereby enhance treatment efficacy. In atherosclerosis, macrophages ingest ox-LDL and other materials, resulting in lysosomal accumulation of free cholesterol and cholesteryl esters, which impairs lysosomal function and disrupts acidic pH maintenance.[84,85] As acidic NPs, PLA and PLGA can undergo hydrolysis to produce glycolic and/or lactic acid, directly restoring lysosomal acidity and function.[74] Zhang et al assessed the capacity of PLA and PLGA to ameliorate macrophage lysosomal dysfunction through both in vivo and in vitro studies. Experiments in cultured macrophages revealed that PLGA NPs were particularly effective at targeting and acidifying lysosomes, whereas PLA did not affect acidification. In ApoE$^{-/-}$ mice fed a Western diet, treatment with PLGA NPs reduced the complexity of aortic root lesions, as evidenced by decreased cell apoptosis, reduced necrotic core formation, diminished cytotoxic protein aggregation, and increased fibrous cap formation.[74] These results underscore the therapeutic potential of acidic NPs, especially those based on PLGA, in addressing macrophage lysosomal dysfunction associated with AS.

In addition to conventional carrier-based delivery systems, carrier-free drug self-delivery systems have emerged in recent years as promising strategies for achieving theranostic nanoplatforms for AS. Chen et al developed an indole molecule-templated self-assembly method to prepare probucol (PB) nanomedicines tailored for atherosclerotic theranostics. This PB-based nanomedicine not only neutralized ROS but also exhibited anti-inflammatory properties and inhibited macrophage foam cell formation. The theranostic functionality was enhanced by the ability of indole molecules to be used for fluorescence imaging.[71] Wu et al designed a study focusing on tannic acid-poloxamer self-assembled nanoparticles (TPNPs) for the treatment of advanced AS. In vitro experiments demonstrated that TPNPs could effectively inhibit inflammatory responses and modulate macrophage polarization. In vivo studies further demonstrated that TPNPs could reduce the production of ROS and promote the polarization of M2 macrophages, leading to significant alleviation of advanced atherosclerotic plaques. Given their advantages, including low cytotoxicity, straightforward synthesis, and multifunctionality, TPNPs hold great promise as an intervention platform not only for AS but also for other inflammation-related diseases[32] (Figure 4).

Active Targeting

Scavenger Receptors

Scavenger receptors are prominently overexpressed on the surface of activated macrophages. During the pathological progression of atherosclerosis in its early stages, the overexpression of class A scavenger receptors (SR-A) on macrophages is particularly significant.[17] Leveraging this observation, Bai et al designed microRNA-146a-coated superparamagnetic iron oxide NPs (miR-146a-SPIONs).[86] The outer layer of these NPs consists of miR-146a oligonucleotides, which naturally bind to SR-A receptors on macrophages and endothelial cells within atherosclerotic plaques, promoting the internalization of NPs by cells without the need for additional targeting ligands, thus achieving targeted drug delivery. The in vivo distribution of miR-146a-SPIONs was rigorously validated via various experimental techniques, including inductively coupled plasma mass spectrometry (ICP-MS), fluorescence imaging, and flow cytometry. The results indicated that the accumulation of miR-146a-SPIONs in the aorta and heart was significantly higher compared to PEG-SPIONs. Moreover, miR-146a-SPIONs exhibited stronger binding to macrophages and endothelial cells in the aorta, particularly to cells rich in SR-A, with the liver also being one of the main accumulation sites. These findings confirmed the ability of miR-146a to actively target macrophage scavenger receptors. When miR-146a-SPIONs were administered to ApoE$^{-/-}$ mice fed a high-cholesterol diet, qRT-PCR analysis revealed that miR-146a-SPIONs significantly reduced the expression of genes associated with the NF-κB pathway in the aorta, demonstrating their anti-inflammatory effects. In addition, miR-146a expression in the aorta was increased, confirming its gene regulatory action in vivo. Further evidence from Oil Red O staining indicated that miR-146a-SPIONs have therapeutic potential in improving atherosclerotic plaques. CD36, a membrane glycoprotein and member of the class B scavenger receptor family, is expressed on macrophages and plays a role in promoting foam cell formation upon the uptake of ox-LDL.[87] Wang et al engineered

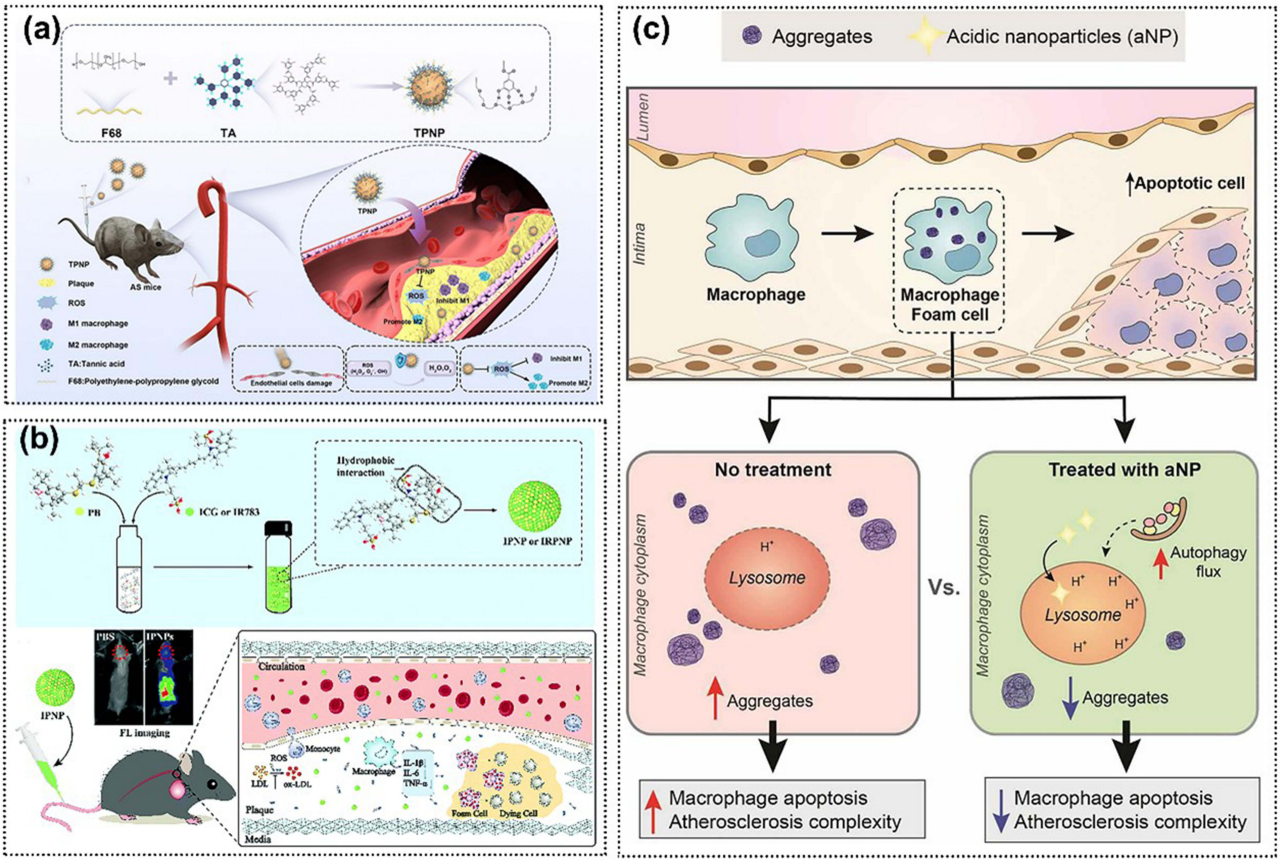

Figure 4 Passive Targeting strategies for the treatment of Atherosclerosis. (**a**) Schematic illustration of the synthesis procedure and the anti-atherosclerotic impacts for TPNP. Reprinted from Wu H, Sheng J, Wang Z, et al. Tannic acid-poloxamer self-assembled nanoparticles for advanced atherosclerosis therapy by regulation of macrophage polarization. J Mat Chem B. 2024;12:4708–4716. doi:10.1039/D3TB01157G. Copyright 2024, Royal Society of Chemistry.[32] Copyright 2024, Royal Society of Chemistry. (**b**) Preparation of PB nanoparticles templated by indole molecules via hydrophobic interactions (IPNP or IRPNP) to serve as a smart theranostic agent for atherosclerosis, administered i.v. to eliminate ROS, reduce inflammatory cytokine expression, and enable FL imaging. Reprinted from Chen F. Theranostics of atherosclerosis by the indole molecule-templated self-assembly of probucol nanoparticles. J Mater Chem B. 2021;9:4134–42. Copyright 2021, Royal Society of Chemistry.[71] Copyright 2021, Royal Society of Chemistry. (**c**) Overview of how acidic nanoparticles contribute to stabilizing atherosclerotic plaques. Reprinted from Zhang X, Misra SK, Moitra P, et al. Use of acidic nanoparticles to rescue macrophage lysosomal dysfunction in atherosclerosis. Autophagy. 2023;19(3):886–903. doi:10.1080/15548627.2022.2108252. Copyright 2022, Taylor & Francis.[74]

a nanomedicine based on composite mesoporous silica NPs (CMSNs) that incorporated the SIRT1 activator SRT1720 and targeted macrophages with high CD36 expression via anti-CD36 antibodies to increase therapeutic efficacy. Both in vitro and in vivo studies confirmed the excellent targeting ability of CMSN@SRT@Anti. Notably, coculture experiments involving RAW264.7 cells and ox-LDL-stimulated RAW264.7 cells with CMSN@SRT@Anti revealed stronger fluorescence in ox-LDL-stimulated cells, potentially due to increased CD36 expression after ox-LDL treatment.[88] These experiments, which spanned the molecular, cellular, and whole-animal levels, comprehensively validated the targeting specificity of CMSN@SRT@Anti. In addition to anti-CD36 antibodies, oxidized phospholipids can serve as ligands targeting CD36. Craparo et al selected KOdia-PC as a key component for targeting CD36 and validated its effective targeting properties through in vitro cellular experiments[89] (Figure 5).

Mannose Receptor

Macrophages harbor various carbohydrate receptors, including the macrophage galactose-binding lectin (MGL, CD301) and the mannose receptor (MR, CD206).[92] Chen et al investigated the targeting potential of macrophages by decorating NPs with mannose, galactose, and dextran. They co-cultured Cy5.5-labeled NPs with RAW 264.7 macrophages and evaluated the percentage of Cy5.5-positive cells and mean fluorescence intensity (MFI) using flow cytometry. These findings revealed that NPs modified with mannose and dextran were more effective at increasing the transfection

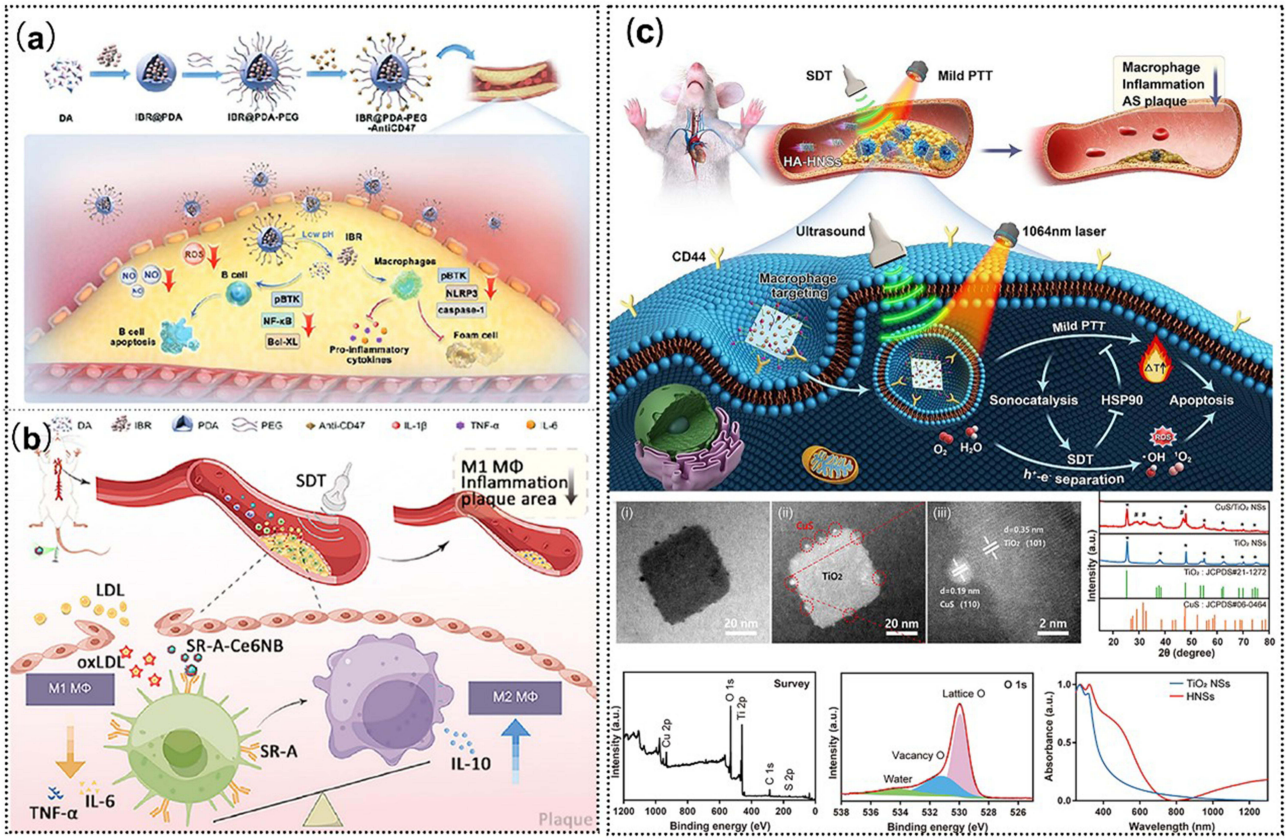

Figure 5 Active targeting Strategies for the treatment of atherosclerosis. (**a**) IBR@PDA-PEG-AntiCD47 facilitates atherosclerosis treatment by regulating B cells and macrophages. Reprinted from Wang H, Zhao R, Peng L, et al. A dual-function CD47-targeting nano-drug delivery system used to regulate immune and anti-inflammatory activities in the treatment of atherosclerosis. Adv Healthcare Mater. 2024;13:e2400752. doi:10.1002/adhm.202400752. Copyright 2024, Wiley-VCH.[90] (**b**) SR-A-Ce6NB-driven SDT facilitates the transition of macrophages from the M1 to M2 phenotype, achieving both anti-inflammatory and anti-atherosclerotic effects. Reprinted from Chen Y, Wang H, Pan J, et al. Macrophage-targeted ultrasound nanobubbles for highly efficient sonodynamic therapy of atherosclerotic plaques by modulating M1-to-M2 polarization. Atherosclerosis. 2024;389:117423. doi:10.1016/j.atherosclerosis.2023.117423. Copyright 2024, Elsevier.[91] (**c**) Schematic illustration of HNSs. Reprinted from Cao Z, Yuan G, Zeng L, et al. Macrophage-targeted sonodynamic/photothermal synergistic therapy for preventing atherosclerotic plaque progression using CuS/TiO(2) heterostructured nanosheets. ACS nano. 2022;16:10608–10622. doi:10.1021/acsnano.2c02177. Copyright 2022, American Chemical Society.[14]

efficiency, with mannose-modified NPs being particularly effective at targeting macrophages.[64] He et al employed a refined mannose-decorated dendrimeric nanoparticle system for targeted macrophage therapy, achieving dual delivery of SR-A siRNA to lower LDL uptake and LXR-L to increase cholesterol efflux.[93] In vivo experiments using LDLR-deficient mice demonstrated that the treatment specifically reduced SR-A expression and increased ABCA1 and ABCG1 levels within atherosclerotic plaques in the aortic arch without affecting other tissues. The treatment also resulted in reduced plasma triglycerides and a significant decrease in plaque area and cholesterol levels in the aortic arch compared with those in the control group. Current evidence suggests that MRs are predominantly expressed in M2 macrophages, whereas their expression is either minimal or suppressed in M1 macrophages.[94] In addition, Chen et al developed a novel and highly selective MR-targeting ligand and explored its potential for selectively targeting M2 macrophages for nanoparticle delivery. Confocal microscopy analysis revealed significantly greater mannose receptor targeting ligand (MRTL) uptake in M2 macrophages than in resting and M1 macrophages, with 2.4-fold and 11.8-fold increases, respectively. This research confirms the viability of MRTL-mediated M2 targeting, paving the way for in vivo studies.[95]

CD44

A substantial body of research indicates that the transmembrane glycoprotein CD44 is upregulated in activated macrophages and has a high affinity for HA.[96] −,-Epicatechin gallate (ECG) has been shown to inhibit macrophage foam cell formation and suppress the abnormal proliferation of vascular smooth muscle cells (VSMCs), suggesting its potential as an anti-

atherosclerotic agent.[97] However, its poor biostability and rapid metabolism have limited its clinical application.[98] To address these challenges, Yu et al leveraged the inclusion capacity and functional modification properties of β-cyclodextrin (β-CD) to design and synthesize pH-responsive acetalized β-CD (PH-CD) and CD44-targeted HA-cyclodextrin (HA-CD) dual-carrier nano-drug delivery systems,[99] which encapsulate ECG to increase its stability and achieve targeted delivery for the treatment of AS. In vitro experiments using ox-LDL-induced macrophages demonstrated that, compared with free ECG, drug-loaded NPs significantly suppressed the expression of TNF-α, IL-6, and ROS in macrophages. In addition, the NPs altered the cell cycle distribution, reduced apoptosis, promoted macrophage migration, and decreased the expression of ox-LDL receptor proteins. In an $ApoE^{-/-}$ mouse model of AS induced by a high-fat diet, treatment with ECG-NPs improved blood lipid levels, reduced hepatic lipid accumulation, and regulated the expression of cholesterol metabolism-related genes. Notably, dual-NPs were more effective than free ECG in regulating blood lipid abnormalities and hepatic lipid accumulation while also reducing the expression of serum inflammatory mediators. Both in vitro and in vivo experiments confirmed that this nano-platform exhibits excellent biosafety.

Stabilin-2 Receptors

In atherosclerotic lesions, the expression of stabilin-2 on the surface of macrophages is significantly upregulated, positioning stabilin-2 as a critical target for macrophage-specific interventions in diseased areas. The stabilin-2 targeting peptide (S2P) can specifically target stabilin-2. Black phosphorus nanosheets (BPNSs) have attracted considerable attention in nanomedicine because of their superior biocompatibility. Recent studies have demonstrated that BPNSs can effectively scavenge ROS and suppress the production of atherosclerosis-related inflammatory factors in macrophages at lesion sites. He et al adopted a "drug delivery" strategy, synthesizing BPNSs via liquid-phase exfoliation and modifying their surface with S2P-PEG-NH_2 to obtain BPNSs@PEG-S2P. The anti-inflammatory drug Resolvin D1 was loaded onto BPNSs by leveraging their two-dimensional layered structure, thereby constructing a targeted drug delivery nanosystem.[100] Using a chelator-free method, they administered ^{64}Cu-labeled BPNSs@PEG-S2P/R via tail vein injection to atherosclerotic $ApoE^{-/-}$ mice. The results showed that BPNSs@PEG-S2P/R exhibited a half-life of 84.4 minutes in the bloodstream, with initial high uptake in macrophage-dense organs such as the spleen and liver, which decreased over time. Radioactivity increased in metabolic organs, and aortic accumulation was significantly greater than that in the other groups, which correlated with stabilin-2 expression. Enhanced aorta accumulation was observed via near-infrared fluorescence imaging, confirming the targeting of macrophages with stabilin-2. These results confirm the feasibility of targeting macrophages with stabilin-2 as a target. Epsins, a family of evolutionarily conserved proteins involved in endocytosis, have emerged as key regulators of various cellular functions. Cui et al employed single-cell RNA sequencing combined with an innovative computational approach, to elucidate the role of Epsins in modulating cholesterol metabolism and efflux in macrophages. Their research demonstrated that Epsins could enhance lipid internalization through CD36 while suppressing cholesterol transport via ABCG1. By employing an S2P-modified nanoparticle system for Epsin siRNA delivery, the suppression of Epsins in inflamed macrophages could curb inflammation, slow the progression of AS, and promote the resolution of atherosclerotic lesions. Notably, their experiments, which included both female and male mice, revealed no sex-based differences in outcomes, suggesting that the therapeutic effects of Epsin targeting are sex independent. This work offers novel insights and a potential therapeutic avenue for AS management.[101]

Folate Receptor

An increasing number of studies have reported elevated folate receptor (FR) expression in atherosclerotic lesions.[102,103] Notably, FR expression is significantly upregulated in activated macrophages compared with their nonactivated counterparts and is largely absent in most healthy tissues.[104] Yao et al engineered a novel dual-modal imaging agent, MNPs@OPE-PEG-FA, designed to target activated macrophages within atherosclerotic plaques by utilizing folic acid as a receptor-specific ligand.[105] Compared with a nontargeted control, this agent demonstrated superior cellular uptake in FR-positive RAW264.7 macrophages in vitro, a finding that was further validated in $ApoE^{-/-}$ mice with AS induced by carotid artery ligation. Post-administration MRI analysis of MNPs@OPE-PEG-FA revealed a marked reduction in signal intensity within the plaque regions, indicating effective targeting for imaging purposes. Furthermore, the two-photon

fluorescence capability of these NPs enables a dual-modal diagnostic approach, allowing both in vitro and ex vivo detection of atherosclerotic plaques. These findings highlight the potential of this agent for noninvasive characterization of atherosclerotic lesions.[105]

Other Receptors

In addition to the aforementioned targeting receptors, the expression of molecules such as IL-1R[106] and integrin αvβ3[107] on the surface of macrophages within plaques is also upregulated. This upregulation allows for macrophage-specific targeting by leveraging these highly expressed receptors. Furthermore, CD47, which functions as a "do not eat me" signal, is expressed on the surface of apoptotic cells in plaques. It interacts with signal regulatory protein-α (SIRPα) on macrophages, thereby inhibiting the clearance of apoptotic cells by macrophages.[108] To address this, Luo et al designed bifunctional polydopamine NPs.[109] These NPs serve a dual purpose: first, they modulate the CD47-SIRPα phagocytic signaling axis by incorporating surface-modified anti-CD47 antibodies, which restore macrophage efferocytosis. Second, they encapsulate NLRP3 inhibitors (CY-09) to regulate intracellular inflammatory responses in macrophages, thereby reducing the secretion of the inflammatory cytokine IL-1β. This dual approach achieves a synergistic therapeutic effect, targeting both extracellular and intracellular mechanisms and effectively restoring macrophage function (Table 3).

Controllable Release of Nanomedicines

Upon reaching the target site, drug release should be triggered by external or internal stimuli (such as pH, light, sound, enzymes, etc), ensuring that the drug is released on demand at the target site, maintaining an effective therapeutic concentration and avoiding the waste and adverse reactions caused by premature drug release (Table 4).

ROS-Responsive Release

Atherosclerosis progression is characterized by an overexpression of ROS in tissues, driven by the inflammatory response of macrophages and mitochondrial oxidative stress.[123,133] NPs featuring ROS-responsive structures can be designed to not only enable plaque imaging[123] but also trigger drug release in the plaque microenvironment for the treatment of AS.[125,134]

Recent studies have revealed the expression of Olfactory Receptor 2 (Olfr2) in mouse vascular macrophages, which is associated with activation of the NLRP3 inflammasome.[135] Consequently, Ni et al developed a nanocarrier to deliver small interfering RNA targeting Olfr2 (si-Olfr2) to macrophages to dampen NLRP3 inflammasome activation and reduce IL-1β release by downregulating Olfr2 expression.[123] The nanocarrier incorporates an ROS-responsive core composed of the oligomer oDHLA, which encapsulates the siRNA complexed with the ionizable lipid-like compounds G0-C8. This ROS-responsive core enables controlled drug release in the presence of elevated ROS levels. The nanoparticle is further coated with an amphiphilic organic semiconductor polymer (SP-PEG), which not only shields the nanostructure but also enables photoacoustic imaging within the NIR-II window. By modulating SP-PEG levels, the photoacoustic signal can be tailored for enhanced atherosclerotic plaque visualization. In addition to the aforementioned ROS-responsive nanocarriers, Wu et al introduced an innovative approach termed "carrier-free nanomedicines",[124] which addresses the limitations associated with traditional nanocarriers, including suboptimal drug loading and incomplete release, thereby increasing drug bioavailability. Moreover, the intravenous administration route circumvents the hepatic first-pass effect commonly encountered with oral administration. These carrier-free nanomotors are powered by NO generated through the reaction between L-arginine and phosphatidylserine (PS). The nanomotors exhibit a dual-targeting mechanism: they first navigate toward atherosclerotic plaques by leveraging the high ROS and inducible nitric oxide synthase (iNOS) expression in the plaque microenvironment, thereby achieving initial plaque targeting. Subsequently, by mimicking the "eat me" signal through PS, they precisely target macrophages within the plaque, achieving a second level of specificity. Furthermore, these nanomotors can scavenge ROS, contributing to their therapeutic efficacy. By adopting this carrier-free nanomotor design, the bioavailability of trehalose has been significantly improved, reducing the required dosage from the previously reported 2.5 g kg^{-1} to 0.01 g $kg^{-}1$.[124]

Table 3 Active Targeting of Macrophages for the Treatment of Atherosclerosis

Receptor	Targeting Ligands	Nanoparticle Platform	Cargo(es)	Cell and(or) Mouse Model	Effects	Ref.
Scavenger Receptor	MicroRNA-146a	PEG-coated SPIONs	miR-146a	RAW 264.7; ApoE-/- mouse model with AS	Suppress the expression of inflammation-related genes.	[86]
	AntiCD36	Ru(bpy)3@SiO2 coated with a mesoporous silica layer (mSiO2)	SRT1720	RAW 264.7; ApoE-/- mouse model with AS	Promote reverse cholesterol transport, inhibit macrophage foam cell formation, and reduce the expression of inflammatory factors.	[88]
	1-(palmitoyl)-2-(5-keto-6-octene-dioyl) phosphatidylcholine (KOdia-PC)	Polycaprolactone (PCL) and poly (N-2-hydroxyethyl)-DL-aspartamide (PHEA)	Rapamycin	RAW 264.7	Inhibit inflammatory immune response and SMC proliferation, prevent monocyte recruitment, and stimulate autophagy.	[89]
	ApoA-I	HDL-like nanoparticles	Ganglioside GM3	RAW 264.7; ApoE-/- mouse model with AS	Inhibit lipid deposition, regulate blood lipid levels, and reduce plaque formation.	[110]
Mannose Receptor	Mannose-PEG-NHS	Dendrimeric NPs	SR-A siRNA; LXR-L	Ldlr-/- mouse model with AS; mouse peritoneal macrophages (MPMs)	Reduce lipid intake and enhance cholesterol efflux.	[93]
	Mannose polymers	Mannan-Grafted Magnetite (Fe_3O_4) Nanoparticles	Simvastatin and niacin	J774A cell; HUVEC	Lower cholesterol and triglycerides, increase HDL, reduce LDL levels, anti-inflammatory, and stabilize plaques.	[111]
	Mannose and triphenylphosphonium	PLGA and encapsulated iron oxide nanoparticles		RAW 264.7; BALB/c mice	Lipid removal property and MRI contrast enhancement.	[112]
	Two mannose molecules and PEG chains	Polycaprolactone (PCL)		Male Sprague–Dawley rats;MPMs	Selectively target M2 MPs.	[95]
	Mannose-PEG-NHS	PAMAM	LXR-L, T0901317	MPMs, Ldlr-/- mouse model with AS	Enhanced cholesterol efflux; anti-inflammatory action.	[113]
CD44	HA	PH-CD and HA-CD	ECG	RAW 264.7; ApoE-/- mouse model with AS	Scavenge of ROS, reduction of inflammatory responses in macrophages.	[99]
	HA-Fc	rHDL	Simvastatin	Mouse aortic endothelial cells (MAECs); RAW 264.7; ApoE-/- mouse model with AS	Promote the efflux of cholesterol and inhibit the secretion of inflammatory factors.	[114]
	HA	CuS/TiO_2		RAW 264.7; ApoE-/- mouse model with AS	Generate ROS; reduce HSP; selectively induce apoptosis of inflammatory macrophages.	[14]
	HA	HA nanoparticles	ATR, rapamycin	LPS-activated RAW264.7 macrophages;TNF-α-activated HUVECs;ApoE-/- mouse model with AS	Antioxidant, anti-inflammatory.	[115]
	HA	Conjugating atorvastatin with HA to form an amphiphilic polymer	ATR	RAW 264.7; ApoE-/- mouse model with AS	Inhibit the expression of inflammatory factors.	[116]
Stabilin-2	S2P	BPNSs	Resolvin D1	LPS-activated RAW 264.7; ApoE-/- mouse model with AS	Anti-inflammatory, antioxidant, and plaque-stabilizing.	[100]
	S2P	Lipid nanoparticles	siRNAs targeting epsins	THP1 Macrophages;ApoE-/- mouse model with AS, PCSK9-AAV8 mouse model with AS	Reduce CD36-mediated lipid uptake and enhance ABCG1-mediated cholesterol efflux.	[101]
	S2P	Polymer-lipid hybrid nanoparticle	siRNA targeting CaMKIIγ	RAW 264.7, HEK-293;Ldlr-/- mouse model with AS	Enhance efferocytosis.	[117]
Folate receptors	FA	Liposome		THP-1; ApoE-/-mice model with AS	Improve targeting specificity and reduce non-specific uptake.	[118]
	FA	Liposome	Betamethasone, BM	RAW 264.7; ApoE-/- mouse model with AS	Anti-inflammatory, anti-proliferative, and regulation of lipid metabolism.	[119]
	FA	SPIONs		RAW 264.7; ApoE-/- mouse model with AS	Targeted dual-modality imaging for monitoring inflammatory plaques and plaque progression.	[105]
	FA	PAMAM	Cyanine 5.5	RAW 264.7; ApoE-/- mouse model with AS	Imaging monitoring.	[120]

Table 4 Controllable Release of Nanomedicines in Plaque

Drug-Release Strategy	Nanoparticle Structure		Cargo(es)	Cell and(or) Mouse Model	Effects	Ref.
	Core	Shell				
pH-Responsive Release	HA nanoparticles		ATR, rapamycin	LPS-activated RAW264.7; TNF-α-activated HUVECs; ApoE-/- mouse model with AS	Antioxidant, anti-inflammatory	[115]
	Polydopamine	PEG and antiCD47	Ibrutinib	RAW 264.7; ApoE-/- mouse model with AS	Inhibit the activation of the NF-κB pathway and NLRP3 inflammasome in macrophages to reduce inflammatory responses.	[90]
	MSNPs	Chitosan and Dextran Sulfate	Rosuvastatin	HUVECs	Anti-inflammatory, antioxidant, and cholesterol-lowering.	[121]
	Metal-organic cage (MOC)-68-doped MnO2 nanoparticles	NH2-PEG	Diallyl trisulfide	THP-1;ApoE-/- mouse model with AS	Reduce the secretion of IL-1β, suppress the expression of HIF-1α, and inhibit the formation of M1 macrophages and foam cells.	[122]
ROS-Responsive Release	ROS-responsive oligomer (o-DHLA)	Amphiphilic organic semiconductor polymer (SP-PEG)	Si-Olfr2	RAW 264.7; ApoE-/- mouse model with AS	Inhibit the activation of the NLRP3 inflammasome and the secretion of IL-1β.	[123]
	β-CD-anchored discoidal rHDL	HA-Fc	Simvastatin	MAECs; RAW 264.7; ApoE-/- mouse model with AS	Promote the efflux of cholesterol and inhibit the secretion of inflammatory factors.	[114]
	Tr-Arg NPs	Phosphatidylserine	Trehalose	HUVECs, RAW 264.7; ApoE-/- mouse model with AS	Regulate the M2 polarization of macrophages.	[124]
	PMMP	RBC membrane	Lipid-specific fluorophore and a prednisolone (Pred)-based prodrug polymer	RAW 264.7; ApoE-/- mouse model with AS	Precisely localize and monitor plaques both in vitro and in vivo, inhibit the production of inflammatory mediators, stabilize plaques, and prevent their rupture.	[125]
	Amphiphilic, oxidation-sensitive chitosan oligosaccharides (Oxi-COS)	Macrophage membrane	Atorvastatin	RAW 264.7; ApoE-/- mouse model with AS	Lipid-lowering, anti-inflammatory, and plaque-stabilizing effects; improvement of vascular endothelial function.	[16]
Enzyme-Responsive Release	Mannan-Grafted Magnetite (Fe_3O_4) Nanoparticles, MN-MNPs	Mannan	Simvastatin and niacin	J774A cell; HUVEC	Lower cholesterol and triglycerides, increase HDL, reduce LDL levels, anti-inflammatory, and stabilize plaques.	[111]
	PLGA-Pep-PEG and PLGA-PEG-c(RGDfC) (a targeting polymer)		Rapamycin	HUVECs, RAW264.7, ApoE-/- mouse model with AS	Anti-inflammatory, promote autophagy, stabilize plaques.	[107]
	MSNs	CD9-antibody	Rosuvastatin	RAW 264.7, MS1 cell; ApoE-/- mouse model with AS	Senescent cell clearance.	[126]

(*Continued*)

Table 4 (Continued).

Drug-Release Strategy	Nanoparticle Structure		Cargo(es)	Cell and(or) Mouse Model	Effects	Ref.
	Core	Shell				
Cholesterol-Responsive Release	The core is composed of an inclusion complex of methyl-β-cyclodextrin and simvastatin, and the shell is made of phospholipids.		Simvastatin	J774A.1, RAW264.7;ApoE-/- mouse model with AS	Reduce the cholesterol load in macrophages, decrease their activation and proliferation, and stabilize plaques.	[127]
Sound-Responsive Release	Curcumin nanosuspensions (Cur-ns)	Polyvinylpyrrolidone (PVPK30) and sodium dodecyl sulfate	Curcumin	RAW 264.7; ApoE-/- mouse model with AS	Enhance macrophage apoptosis and inhibit plaque progression by interfering with macrophage polarization.	[18]
	CuS/TiO2 nanosheets	HA and PEG		RAW 264.7; ApoE-/- mouse model with AS	Generate ROS; reduce HSP; selectively induce apoptosis of inflammatory macrophages.	[14]
	Nanobubbles	PP1 peptide	Ce6	RAW 264.7; ApoE-/- mouse model with AS	Promote the polarization from M1 to M2 macrophages; promote macrophage apoptosis, and autophagy, or enhance phagocytosis.	[91]
	Gold Nanoparticles functionalized with the methyl ester of aminolevulinic acid (MALA)	PEG		THP-1	Induce macrophage apoptosis	[128]
Light-Responsive Release	IR780-Gd-OPN nanomicelles			RAW 264.7; ApoE-/- mouse model with AS	Inhibit NF-κB signaling pathway, regulate lipid metabolism, and macrophage polarization to reduce inflammatory responses.	[129]
	CuCo2S4 nanocrystals		Chloroquine	RAW 264.7; ApoE-/- mouse model with AS	Absorb light energy and convert it into heat, cause thermal damage to macrophages; anti-inflammatory.	[130]
	DS conjugated with Ce6			RAW 264.7; ApoE-/- mouse model with AS	Induce efferocytosis.	[131]
	A carbon nanocage (CNC) core	Chitosan (CS) and Dextran Sulfate, DS	Ce6	RAW 264.7; ApoE-/- mouse model with AS	Reduce the secretion of inflammatory factors, induce apoptosis, and inhibit inflammation and cell proliferation.	[17]
	UCNPs	Mesoporous silica	Calcium regulators	RAW264.7; pig	Promote the polarization of macrophages towards M2 type.	[132]

pH-Responsive Release

Owing to the presence of a significant number of inflammatory cells within atherosclerotic plaques, which exhibit high metabolic activity in their activated state, these cells predominantly utilize glycolysis instead of oxidative phosphorylation to produce energy, a characteristic referred to as the Warburg effect.[136] In addition, localized restrictions in blood flow contribute to hypoxic conditions, further enhancing cellular glycolysis. The substantial accumulation of lactate produced through this process lowers the pH.[137]

Leveraging the acidic pH properties of atherosclerotic plaques, pH-responsive NPs have been designed for precise drug release. Cheraga et al developed a pH-sensitive nanoconjugate composed of all-trans-retinal (ATR) and HA, resulting in HR NPs with a core–shell structure tailored for targeted therapy of atherosclerotic plaques.[115] The HA shell and ATR core ensure stability at physiological pH while enabling the release of ATR in the slightly acidic environment of plaques, where it exerts antioxidant effects. Furthermore, HR NPs encapsulate rapamycin (RAP), which is released within plaques to exert local anti-inflammatory and anti-proliferative effects, inhibiting AS progression. In studies using atherosclerotic model mice ($ApoE^{-/-}$ mice), treatment with HRRAP NPs significantly reduced the lesion area of the entire aorta. Compared with that in the saline control group, the lesion area in the HRRAP NP treatment group decreased to an average of 10.2%, which was significantly different from that in the group treated with RAP alone. Moreover, HRRAP NPs demonstrated enhanced safety and tolerability during long-term treatment periods.[115] In addition to covalent linkages, metal-organic cages can also undergo pH-dependent conformational changes. Leveraging this property, Li et al used MOC-68 as a carrier to load diallyl trisulfide (DATS). The binding between MOC-68 and DATS weakened under acidic conditions, and the subsequent reaction with H_2O_2 further promoted the dissociation of DATS to release H_2S.[122]

Enzyme-Responsive Release

In addition to the presence of highly active ROS and lower pH levels, the activities of specific enzymes at the plaque site can also regulate drug release. Notably, the high expression of Cathepsin K (CTSK) within arterial plaques[138] has attracted significant interest. Further studies have revealed that CTSK is actively involved in the initiation and progression of AS, contributing to the formation of vulnerable plaques. Moreover, CTSK exhibited peak enzymatic activity in acidic environments. Given these findings, CTSK is considered a promising trigger for controlled drug release in the context of AS. Fang et al designed a targeting polymer for integrin αvβ3 (PLGA-PEG-c) and a CTSK-sensitive polymer (PLGA-Pep-PEG), which self-assembled to form NPs with both targeting ability and responsiveness capable of encapsulating RAP.[107] Upon reaching the atherosclerotic lesion area, these NPs are cleaved under the action of CTSK, thereby releasing the encapsulated drugs for therapeutic purposes. Similarly, hyaluronidase (HAase) is another highly expressed enzyme in the plaque microenvironment. Leveraging this, Pham et al coated the surface of NPs with HA. In vitro experiments were conducted by adding HAase to buffer solutions at pH 5.0 and 7.4, followed by monitoring drug release from CD9-HMSN@RSV NPs. The results demonstrated a significant increase in the release of RSV and CD9 antibodies in the presence of HAase, particularly under acidic pH conditions that mimic the atherosclerotic lesion environment.[126] These findings indicate that the presence of HAase significantly promotes the release of drugs from CD9-HMSN@RSV NPs, confirming the responsiveness of the nanoparticle system to HAase, which is highly important for achieving targeted drug delivery in the atherosclerotic lesion area. On the other hand, intracellular enzymes can also serve as effective triggers for drug release. For example, Rastegari et al utilized mannose-modified magnetic NPs as drug carriers, enabling the controlled release of simvastatin and niacin through an enzyme-responsive mechanism.[111] These NPs are recognized by mannose receptors on macrophages, leading to their internalization into lysosome-rich cellular compartments. Within lysosomes, mannose hydrolase degrades the mannose layer, thereby releasing the encapsulated drugs. In vitro experiments revealed that in the presence of mannan hydrolase, NPs released 79.51% of simvastatin and 67.23% of niacin within 90 minutes while maintaining a leakage rate of less than 19.22%, significantly reducing the side effects of systemic administration.[111]

Cholesterol-Responsive Release

While the studies mentioned above effectively utilize abnormal microenvironments to control drug release, research that simultaneously aims to normalize these abnormal microenvironments is relatively scarce. By building on the high-cholesterol environment characteristic of plaques, Kim et al leveraged the high affinity of methyl-β-cyclodextrin for cholesterol to design cargo-switching NPs (CSNPs).[127] CSNPs release simvastatin when it binds to cholesterol, as cholesterol binds more tightly to cyclodextrin. This allows CSNPs to replace simvastatin with cholesterol, facilitating the removal of cholesterol through a cargo-switching process. Confocal microscopy experiments revealed that, in vitro, CSNPs engage with cholesterol deposits within 5 minutes at 37°C, confirming their ability to pinpoint these deposits. In $ApoE^{-/-}$ mice with AS, CSNP treatment notably decreased plaque in the aortic root, curve, and upper section, demonstrating clear therapeutic benefits regardless of dietary conditions. Compared with those at baseline, mice fed a regular diet presented more pronounced plaque reduction in the aortic root and curve following CSNP treatment, whereas those fed a high-fat diet presented plaque reduction primarily in the root area. These findings suggest that the targeted anti-inflammatory action of CSNPs can effectively complement systemic cholesterol reduction to promote plaque shrinkage. Moreover, CSNP treatment does not adversely affect body weight, induce liver toxicity, or alter plaque vulnerability.[127]

Photodynamic and Photothermal Therapies

In recent years, phototherapy, such as photodynamic therapy (PDT) and photothermal therapy (PTT), has emerged as a promising treatment strategy for AS.[130,139,140] Both modalities utilize light energy to achieve therapeutic effects: PDT generates ROS by activating photosensitizers, which subsequently induce macrophage death,[141] whereas PTT employs photothermal agents to absorb light energy and convert it into heat, thereby inducing the thermal ablation of macrophages.[142] Despite their potential, current phototherapy approaches face certain limitations and challenges. One significant concern in PDT is the selection of photosensitizers, as their nonspecific binding to vascular structures may exacerbate vascular wall damage and potentially worsen the progression of AS.[143] Accordingly, the development of photosensitizers that specifically target plaque macrophages is essential. Song et al conjugated dextran sulfate with the photosensitizer chlorin e6 to create an NIRF-emitting phototherapy agent. This agent specifically targets SR-A, which is highly expressed in activated macrophages.[131] By employing a customized laser system for localized irradiation, this approach enables the precise treatment of target lesions while minimizing collateral damage to surrounding healthy tissues.

Second, traditional phototherapy reduces plaques by inducing cell apoptosis; however, excessive apoptosis may increase the risk of plaque instability and rupture.[144,145] To address this limitation, He et al developed an innovative approach utilizing IR780-Gd-OPN nanomicelles.[129] This nanomicelle-mediated mild phototherapy demonstrated a protective effect on foam cells by preventing apoptosis through the activation of HSP27 and the inhibition of the NF-κB pathway, thereby regulating lipid metabolism, macrophage polarization, and reducing inflammatory responses. In addition, mild phototherapy maintains a controlled, low temperature, minimizing thermal damage to surrounding healthy tissues. As a result, this method yields significantly lower toxicity and greater biocompatibility compared to conventional photothermal therapy.

Sonodynamic Therapy

Sonodynamic therapy (SDT) has evolved from photodynamic therapy and possesses stronger penetration capabilities[146] and more precise targeting[91] than its optical counterpart. SDT activates sonosensitizers that accumulate in plaques through low-frequency ultrasound stimulation, generating ROS to induce apoptosis in target cells.[14,147] However, SDT faces challenges such as insufficient accumulation of sonosensitizers and low rates of ROS production. To address these issues, Chen et al employed nanobubbles as carriers to encapsulate Ce6, increasing its accumulation and stability at the lesion site. Concurrently, they utilized low-intensity pulsed ultrasound, which can trigger this nanoplatform to produce more ROS, thereby amplifying the effects of SDT[91] (Figure 6).

Multi-Responsive Drug Delivery Systems

The application of stimulus -responsive nanosystems in atherosclerosis treatment has shown promise; however, conventional single-stimulus systems, which rely solely on pH, ROS, or enzymatic triggers, face inherent limitations in addressing the

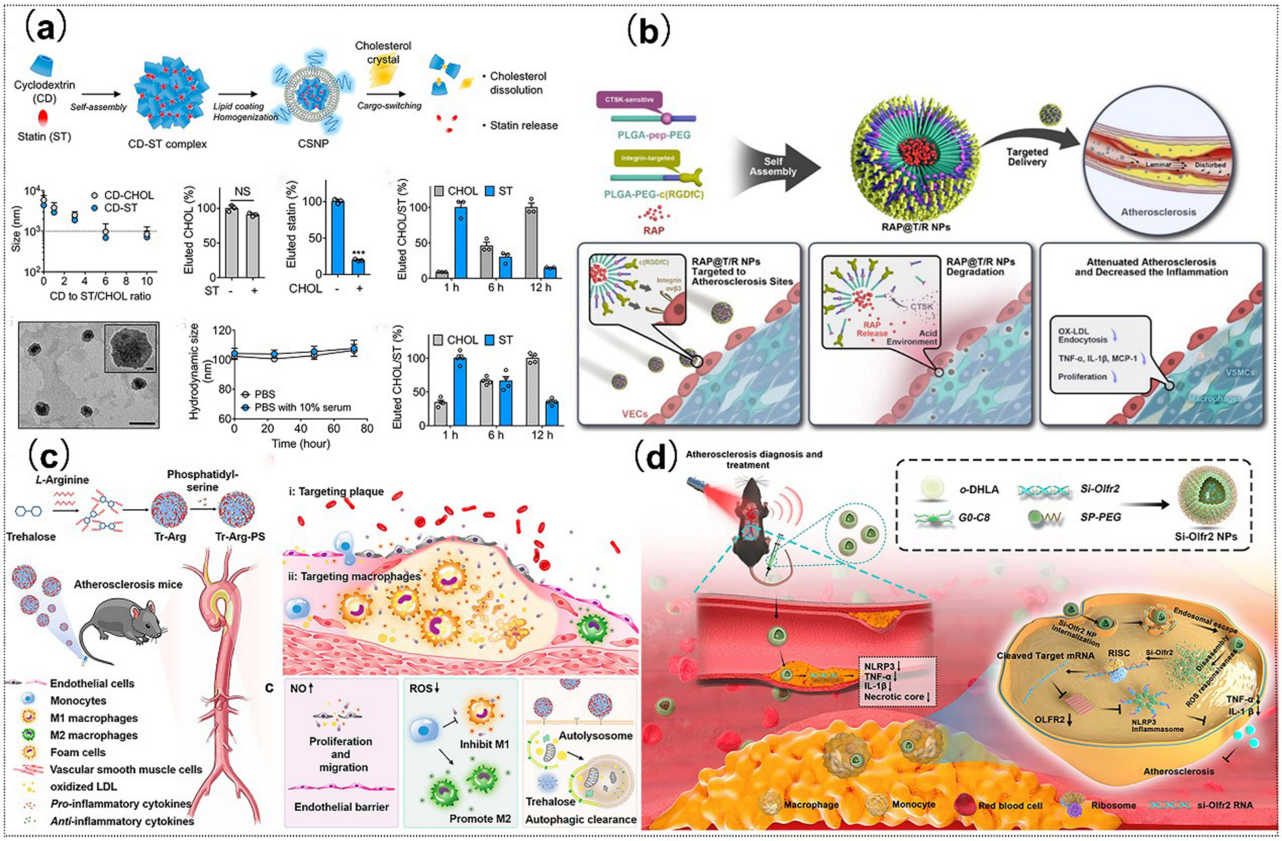

Figure 6 Controllable Release of Nanomedicines under the specific microenvironment of plaques. (**a**) Fabrication and characterization of physicochemical attributes of cargo-switching nanoparticles (CSNP). Reprinted from Kim H, Kumar S, Kang D-W, et al. Affinity-driven design of cargo-switching nanoparticles to leverage a cholesterol-rich microenvironment for atherosclerosis therapy. ACS Nano. 2020;14(6):6519–6531. doi:10.1021/acsnano.9b08216. Copyright 2020, American Chemical Society.[127] (**b**) Schematic diagram of the formation process of RAP@T/R nanoparticles and their targeted delivery of RAP for atherosclerosis treatment, activated by CTSK. Reprinted from Fang F, Ni Y, Yu H, et al. Inflammatory endothelium-targeted and cathepsin responsive nanoparticles are effective against atherosclerosis. Theranostics. 2022;12(9):4200–4220. doi:10.7150/thno.70896. Copyright 2022, Ivyspring International Publisher (https://creativecommons.org/licenses/by/4.0/).[107] (**c**) Schematic diagram of the synthesis of Tr-Arg-PS (TAP) nanomotors and their two-stage targeting approach for the comprehensive treatment of AS. Reprinted from Wu Z, Zhou M, Tang X, et al. Carrier-free trehalose-based nanomotors targeting macrophages in inflammatory plaque for treatment of atherosclerosis. ACS Nano. 2022;16(3):3808–3820. doi:10.1021/acsnano.1c08391. Copyright 2022, American Chemical Society.[124] (**d**) Schematic illustration of ROS-triggered si-Olfr2 nanoparticles for atherosclerosis theranostics. Reprinted from Ni H, Zhou H, Liang X, et al. Reactive oxygen species-responsive nanoparticle delivery of small interfering ribonucleic acid targeting olfactory receptor 2 for atherosclerosis theranostics. ACS Nano. 2024;18(34):23599–23614. doi:10.1021/acsnano.4c07988. Copyright 2024, American Chemical Society.[123]

dynamic and heterogeneous nature of the plaque microenvironment. For instance, pathological features such as fluctuating oxidative stress, inflammatory cytokines, and shear stress often render single-signal regulation insufficient, leading to premature drug release, suboptimal targeting, or compromised therapeutic outcomes.[148] Furthermore, advanced atherosclerotic plaques exhibit structural barriers, such as thickened endothelia and narrowed intercellular gaps, which hinder the deep penetration of nanocarriers that rely on passive diffusion or a single driving force.[149] To overcome these challenges, combined stimuli-responsive systems have emerged, integrating multiple pathological signals and external stimuli to achieve spatiotemporal control, enhanced lesion accumulation, and synergistic therapeutic effects.

Wei et al[150] designed a dual-mode-driven nanomotor (Gd-MCNs/Pt-RAPA-AC) that integrates H_2O_2 catalysis and near-infrared (NIR) photothermal propulsion. This system leveraged the endogenous H_2O_2 at inflammatory sites to generate O_2 for self-propulsion, while NIR irradiation enhanced tissue penetration and induced photothermal ablation of macrophages. The asymmetric Pt deposition on mesoporous carbon nanoparticles enabled catalytic decomposition of H_2O_2, alleviating oxidative stress, while rapamycin (RAPA) release counteracts inflammation and promotes autophagy. The dual propulsion mechanisms (chemical and thermal) significantly improved nanoparticle accumulation in plaques, as evidenced by enhanced MRI contrast and reduced lipid deposition in ApoE$^{-/-}$ mice.[150] Similarly, Zhang et al[63] developed a shear force- and cholesterol affinity-responsive nanoplatform (FCD-Se/Res), where β-cyclodextrin (β-CD) was grafted to fucoidan via ROS-sensitive bonds,

enabling targeted drug delivery. The system could actively bind to P-selectin on inflamed endothelium, penetrate plaques under high shear stress, and release resveratrol (Res) via cholesterol competition. Concurrently, ROS-triggered β-CD dissociation facilitated cholesterol efflux, while selenium nanoparticles mitigated oxidative stress. In vivo studies demonstrated a remarkable reduction in plaque vulnerability index (from 4.07 to 0.40) through synergistic regulation of macrophage polarization and lipid metabolism.[63] Both studies highlighted the advantages of multi-stimulus responsiveness. Such integrated systems not only enhance drug bioavailability but also address multiple pathological processes, including inflammation, oxidative stress, and lipid accumulation, within a single therapeutic platform. However, challenges remain in optimizing stimulus sensitivity, minimizing off-target effects, and translating these designs into clinical models that better mimic human atherosclerosis. Future advancements may involve incorporating artificial intelligence for real-time monitoring or combining advanced imaging modalities to guide personalized therapy. Collectively, these innovations highlight the potential of multi-responsive nanosystems to revolutionize atherosclerosis treatment by dynamically adapting to the evolving microenvironment of the plaque.

Macrophage-Associated Biomimetic Nanoparticle Therapy for Atherosclerosis

Despite their therapeutic potential, conventional nanomedicines face rapid immune clearance, hindering clinical translation (Biomimetic Nanocarriers). To address this, CMC@NPs leverage innate "self" markers for immune evasion and prolonged circulation. Crucially, their inherited chemotactic receptors enable active homing to atherosclerotic plaques, while membrane-bound anti-inflammatory factors may locally dampen inflammation. Wang et al developed rapamycin-loaded NPs encapsulated within macrophage membranes (MM/RAPNPs) and explored their feasibility for AS treatment. After the drug was administered to ApoE$^{-/-}$ mice for 30 days and the separated aortas were observed, the results revealed that, compared with free RAP (18.3%) and RAPNPs (14.43%), MM/RAPNPs significantly reduced the atherosclerotic plaque area to 6.59%.[151] The above evidence suggests that biomimetic NPs coated with macrophage membranes could be powerful tools for future AS treatment.

Macrophage membrane properties vary by polarization state: M1 membranes overexpress integrins (eg, α4/β1) for inflammatory site homing, while M2 membranes enhance anti-inflammatory payload delivery. This allows customization for distinct therapeutic goals. Qu et al identified M1 macrophages as pro-inflammatory macrophages, which are capable of more effectively targeting plaques through molecules such as integrins. To achieve this, they induced M1 macrophages by stimulating RAW264.7 cells with LPS, extracted the cell membranes, and developed MM@CD-PBA-RVT, a system designed to respond to and release its payload in a high-ROS microenvironment.[152] On the other hand, Wu et al suggested that M2 macrophages possess greater advantages in anti-inflammatory applications. Consequently, they stimulated RAW264.7 cells with IL-4 to obtain M2 macrophages, utilized their membranes as a coating, and encapsulated PLGA and berberine to create biomimetic NPs (BBR NPs@Man/M2).[153] Both M1-type and M2-type macrophage membranes have demonstrated good plaque-targeting capabilities in atherosclerotic mouse models (Figure 7).

Beyond the utilization of isolated cell membranes for artificial coating, cells naturally secrete a diverse array of membrane-bound extracellular vesicles (EVs), including microvesicles, apoptotic bodies, and exosomes,[154] which inherently possess remarkable capabilities for intercellular communication, targeted delivery, and immunomodulation. These natural biological nanoparticles represent another promising frontier in AS nanotherapy.

Cell-derived extracellular vesicles are characterized by a double-membrane structure and are crucial for intercellular communication. They are intimately linked to vascular oxidative stress and inflammation in AS. In the present study, exosomes derived from various cellular sources were actively explored for their potential in treating AS. For example, endothelial cell-derived exosomes carrying miRNA can regulate macrophage lipid metabolism;[73] platelet-derived exosomes can suppress inflammation;[155] and engineered exosomes can achieve precise control of inflammation by carrying specific molecular anchors to target plaque macrophages,[156] exerting anti-inflammatory therapeutic effects. Furthermore, macrophage-derived exosomes can enhance anti-inflammatory effects and regulate the proliferation and migration of vascular smooth muscle cells.[157] Ji et al designed a self-assembled nanoprobe that specifically recognizes foam cells. This probe is degraded by intracellular hypochlorous acid, releasing a lipophilic fluorophore that integrates into exosomal membranes.[158] This innovative approach enables early detection and continuous

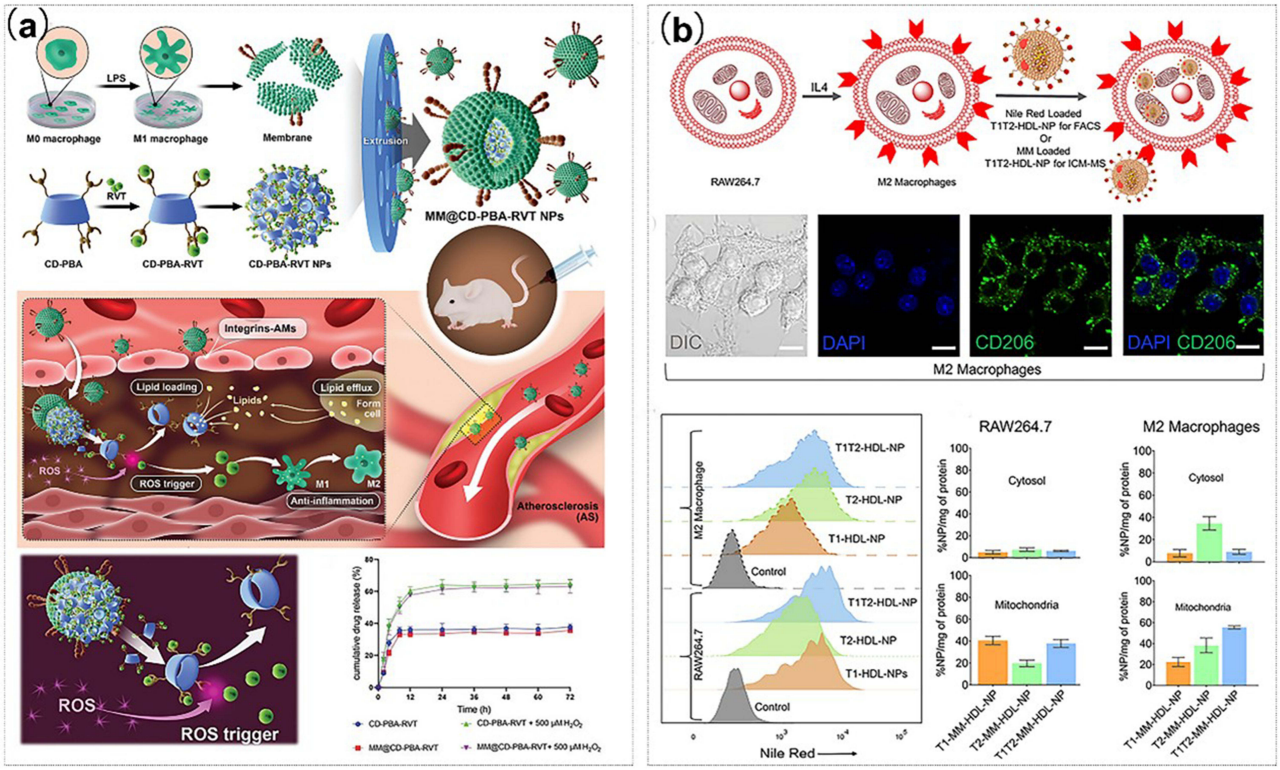

Figure 7 Biomimetic Nanoparticle Therapy for Atherosclerosis. (**a**) Schematic diagram of the synthesis and drug release of MM@CD-PBA-RVT. Reprinted from Qu K, Zhong Y, Zhu L, et al. A macrophage membrane-functionalized, reactive oxygen species-activatable nanoprodrug to alleviate inflammation and improve the lipid metabolism for atherosclerosis management. Adv Healthcare Mater. 2024. doi:10.1002/adhm.202401113. Copyright 2024, Wiley-VCH.[152] (**b**) Schematic representation of the Reprinted from Banik B, Surnar B, Askins BW, et al. Dual-targeted synthetic nanoparticles for cardiovascular diseases. ACS Appl Mater Interfaces. 2020;12(6):6852–6862. doi:10.1021/acsami.9b19036. Copyright 2019, American Chemical Society.[112]

assessment of the risk associated with atherosclerotic lesions, thereby supporting the efficient management of cardiovascular diseases.

Challenges and Prospects

The advent of macrophage-targeted nanotherapies has opened transformative avenues for AS treatment, yet their clinical translation remains encumbered by multifaceted challenges. First, achieving precise and sustained plaque targeting persists as a critical barrier. While pioneering trials, such as the LDL-mimetic paclitaxel-loaded nanoparticles[159] and the CD68-directed photothermal silica-gold nanoparticles (NANOM-FIM trial, NCT01270139[160]), demonstrate lesion-specific delivery, their efficacy is often compromised by off-target accumulation. This arises from the dynamic formation of a protein corona, a layer of adsorbed biomolecules on NP surfaces, that alters receptor-binding specificity and promotes nonspecific uptake in healthy tissues.[30] Furthermore, heterogeneity in scavenger receptor expression across patient populations, influenced by genetic and epigenetic factors, leads to variable therapeutic responses. For instance, in the NANOM-FIM cohort, 30% of patients showed suboptimal CD68-targeted NP uptake due to receptor downregulation in advanced plaques, underscoring the need for adaptive targeting strategies.[160]

Second, biocompatibility and long-term safety profiles of nanomaterials demand rigorous optimization. Superparamagnetic iron oxide nanoparticles exhibit cytotoxicity, causing inflammation, increased membrane permeability, mitochondrial dysfunction, apoptosis, chromosome condensation, ROS generation, and DNA damage.[160,161] Conversely, amorphous silica NPs, initially explored for their inert properties, paradoxically exacerbated arterial inflammation by activating NLRP3 inflammasomes in macrophages, thereby accelerating AS progression in murine

models.[162] A standardized framework for toxicity assessment, integrating high-throughput screening, multi-omics profiling, and advanced in vitro models, is urgently needed to de-risk clinical candidates.

Third, pharmacokinetic limitations hinder therapeutic efficacy, particularly in complex lesions. Rapid renal clearance of small NPs (<10 nm) and hepatic sequestration of larger particles (>200 nm) restrict their residence time in atherosclerotic niches. Besides, the dense fibrous caps of advanced plaques impede NP penetration, necessitating carriers with tunable rigidity or enzyme-responsive surface coatings to enhance diffusivity.

To overcome these limitations, future research should prioritize several aspects. First, comprehensive mechanistic studies are necessary to elucidate the precise interactions of nanomaterials within the body, including their interactions with biomolecules and their influence on disease progression. Second, innovative nanodesign strategies, including the development of novel nanomaterials, the optimization of targeting strategies, the creation of high-specificity targeting ligands or peptides, and the integration of multiple targeting mechanisms, is essential. Moreover, research should focus on interventions at different macrophage targets, screening for low-toxicity nanomaterials, and conducting extensive long-term animal experiments and clinical studies to comprehensively evaluate the long-term safety of nanotechnology in treating cardiovascular and cerebrovascular diseases, with evaluations prioritizing nanomaterials demonstrating favorable toxicity profiles, such as biodegradable polymers or engineered gold nanostructures. Furthermore, optimizing production processes, improving production efficiency, reducing raw material costs, and fostering collaboration in regulatory approvals are crucial to fully unlocking the potential of nanomedicine in treating these diseases, ultimately benefiting patients. Interdisciplinary collaboration across fields such as materials science, computational biology, and regulatory agencies is also critical to streamline scalable production and expedite clinical translation. Machine learning algorithms can accelerate the design of multi-targeted carriers by predicting ligand-receptor interactions, optimizing stimuli-responsive drug release kinetics, and identifying novel biomarkers for precision targeting. AI-driven analysis of multi-omics data may further unravel macrophage heterogeneity in plaques, enabling patient-specific nanotherapy regimens. Moreover, the development of personalized nanotreatment plans tailored to the unique needs and disease characteristics of individual patients represents a significant and promising direction for future research.

Through these comprehensive efforts, we anticipate that nanotechnology will play an increasingly significant role in the treatment of AS, offering patients more effective and safer treatment options. This progress will mark the beginning of a new chapter in the treatment of cardiovascular and cerebrovascular diseases. With the continuous advancement of science and technology, nanomaterials that target macrophages are expected to become important tools for future AS treatment, promoting the development of personalized medicine and precision therapy.

Abbreviations

AS, atherosclerosis; NPs, nanoparticles; PCSK9, proprotein convertase subtilisin/kexin type 9; LDL-C, low-density lipoprotein cholesterol; ApoB-LPs, apolipoprotein B-containing lipoproteins; ox-LDL, oxidized LDL; M-CSF, macrophage-colony stimulating factor; SR-A, scavenger receptor A; TNF-α, tumor necrosis factor-alpha; IL, interleukin; ICAM-1, intercellular adhesion molecule-1; VCAM-1, vascular cell adhesion molecule-1; MMPs, matrix metalloproteinases; LPS, lipopolysaccharide; IFN-γ, interferon-γ; NF-κB, nuclear factor-κB; STAT1, signal transducer and activator of transcription 1; ROS, reactive oxygen species; NO, nitric oxide; EPR, enhanced permeability and retention; LNPs, Lipid-based nanoparticles; SLNs, solid lipid nanoparticles; PAMAM, polyamidoamine; MSNs, mesoporous silica nanoparticles; AuNPs, Gold nanoparticles; SPIONs, superparamagnetic iron oxide nanoparticles; RBCs, red blood cells; rHDL, reconstituted high-density lipoprotein; ABCA1, ATP-binding cassette transporter A1; FDA, Food and Drug Administration; PLA, polylactic acid; PLGA, polylactic-co-glycolic acid,; RSG, radiolabeled rosiglitazone; ApoE, Apolipoprotein E; PB, probucol; ICP-MS, inductively coupled plasma mass spectrometry; qRT-PCR, quantitative reverse transcription polymerase chain reaction; KOdia-PC, 1-palmitoyl,-2-5-keto-6-octene-dioyl, phosphatidylcholine; MFI, mean fluorescence intensity; MR, mannose receptor; MRTL, mannose receptor targeting ligand; ECG, −,-Epicatechin gallate; HA, hyaluronic acid; VSMCs, vascular smooth muscle cells; β-CD, β-cyclodextrin; S2P, stabilin-2 targeting peptide; BPNSs, Black phosphorus nanosheets; FR, folate receptor; SIRPα, signal regulatory protein-α; Olfr2, Olfactory Receptor 2; PAI, photoacoustic imaging; iNOS, inducible nitric oxide synthase; PS, phosphatidylserine; ATR, all-trans-retinal; RAP, rapamycin; MOCs, metal-organic cages; DATS, diallyl trisulfide; CTSK,

Cathepsin K; HAase, hyaluronidase; PDT, Photodynamic Therapy; PTT, Photothermal Therapy; NIRF, near-infrared fluorescence; HSP27, heat shock protein 27; SDT, Sonodynamic Therapy.

Data Sharing Statement

No data was used for the research described in the article.

Funding

This work was supported by the National Natural Science Foundation of China (NSFC), Grant/Award Number: 82471355 and 82171325.

Disclosure

The authors report no conflicts of interest in this work.

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