Harnessing nanomedicine for precise modulation of cardiovascular microenvironment in treatment of cardiovascular diseases

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Abstract: The pathological microenvironment is characterized by inflammation, oxidative stress, and endothelial dysfunction, playing a significant role in the occurrence and development of cardiovascular diseases (CVDs). Therefore, a thorough review of this microenvironment is of vital importance for the development of efficient mechanisms for intervention. In this review, we first introduce the main subtypes of CVDs microenvironment, including vascular injury, myocardial remodeling and atherosclerotic plaque formation. Subsequently, we elaborate with specific examples

on the emerging nanomedicine strategies that target these cardiovascular microenvironment subtypes. Subsequently, we further discuss the applications of emerging nanomaterials in ameliorating cardiovascular oxidative stress, regulating extracellular matrix remodeling, targeting angiogenesis, and modulating the metabolic microenvironment. In particular, we also elaborate on the implementations of numerous stimulus-responsive nanoplatforms in the diagnosis and treatment of the cardiovascular microenvironment. Finally, we discuss the clinical translation of nanomaterials, including the biological safety, targeting, and drug loading rate of these materials. Furthermore, we also outline the future prospects: multi-functional nanosystems, nanoplatforms assisted by artificial intelligence, and personalized nanomedicine. Overall, this review synthesizes current advances in nanomedicine for targeted modulation of the cardiovascular microenvironment, highlighting its therapeutic potential and translational prospects for precision theranostics in CVDs.

Keywords: Nanomedicine, cardiovascular diseases, modulation of pathological microenvironment, precise therapeutics

1. Introduction

Cardiovascular diseases (CVDs) are the leading cause of death and disability worldwide, posing a significant challenge to public health [1-3]. CVDs, including coronary atherosclerotic disease, heart failure, ischemic stroke, and hypertension, represent leading causes of mortality worldwide [4–7]. These diseases share similar pathological pathways, containing chronic inflammation, oxidative stress, non-adaptive fibrosis and dysregulation of angiogenesis [8-9]. Furthermore, these processes gradually deteriorate the structure and function of the cardiovascular system, ultimately leading to irreversible cardiovascular damage and harm to various organs throughout the body [10-12]. Pathological microenvironment remodeling is a prominent feature of CVD, mainly manifested as oxidative stress, cellular dysfunction, and abnormal

angiogenesis [13-14]. The effectiveness of traditional treatment strategies is limited by insufficient tissue targeting and low biological safety [15-17]. Therefore, therapeutic approaches are expected to significantly reduce the clinical burden of CVDs through specific targeting of the pathological microenvironment.

The interaction between cells and molecules in the pathological microenvironment is a critical driving factor for the occurrence of CVDs [18-21]. The main pathological processes of this microenvironment include chronic inflammation, oxidative stress, and endothelial dysfunction [22-24]. For instance, the formation of atherosclerotic plaques is driven by both lipid deposition and the release of inflammatory factors [25-27]. Similarly, ischemia after myocardial infarction can trigger cell necrosis and fibrosis, ultimately leading to deterioration of ventricular function [28-30]. Moreover, acidosis and elevated ROS levels can further exacerbate tissue damage. These pathological changes severely impede the targeted delivery of traditional drugs and the therapeutic effect [31-34]. Therefore, it is crucial to deeply understand these mechanisms and precisely regulate them [35-37].

The microenvironment-targeted therapeutic strategies can act on regions with low pH, oxidative stress, or specific areas rich in proteolytic enzymes related to the disease [38]. Utilizing these characteristics, therapies with stimulus-responsive properties can be designed to achieve specific activation and targeted drug release, thereby enabling precise treatment [39-40]. In recent years, the design of intelligent nanomaterials and their application in diseases have made precise nanomedicine a key strategy for cardiovascular disease intervention [41, 42]. Intelligent nanodrugs actively accumulate at the lesion site by integrating microenvironment-targeting molecules and release drug molecules on demand, thereby synergistically treating CVDs. Particularly, the clinical translation of inorganic and metal-based nanozymes and imaging contrast agents requires strict evaluation of their long-term biocompatibility, biological safety, and tissue metabolic capabilities. Moreover, the development of nucleic acid nanomaterials and biomimetic nanocarriers has significantly expanded the targeted intervention

strategies for disease microenvironments, greatly improving the precise treatment of CVDs [43, 44].

This review provides an in-depth analysis of nanomedicine strategies based on the pathological microenvironment of CVDs, which are utilized for precise treatment of CVDs. Compared with the existing reviews, this review adopts a microenvironment-centered framework, integrating the pathological characteristics of diseases with the design targets and therapeutic mechanisms of nanomedicine. Firstly, we describe the pathological characteristics of the disease microenvironment, including the pathological physiological features of blood vessels, myocardium, and atherosclerotic plaques. Secondly, we systematically explore the mechanisms and design principles involved in nanomedicine regulating these microenvironments, with a focus on targeted intervention strategies for inflammation, oxidative stress, abnormal vascular repair, and metabolic dysfunction. Particularly, we evaluate the clinical application of stimulus-responsive nanotechnology in CVDs. Finally, we discuss the current clinical translation, including bioavailability, targeting utilization, and biological safety, and outline the future prospects, such as multifunctional nanosystems, artificial intelligence-driven nanotechnology, and personalized treatment based on patients (**Fig. 1**).

To clarify the scope of the study, this review defines nanomedicine as a therapeutic or diagnostic system that utilizes nanomaterials or nanocomponents to achieve targeted delivery or responsive regulation of the microenvironment. The relevant platforms are mainly divided into four categories: nano-delivery carriers, active nano-materials, biomimetic systems, and cell-based systems (**Table 1**). These categories are not completely mutually exclusive, as different platforms usually have overlapping functional characteristics. Nanomedicine refers to nano-scale therapeutic components in complex systems, where hydrogels or cells merely serve as supporting scaffolds.

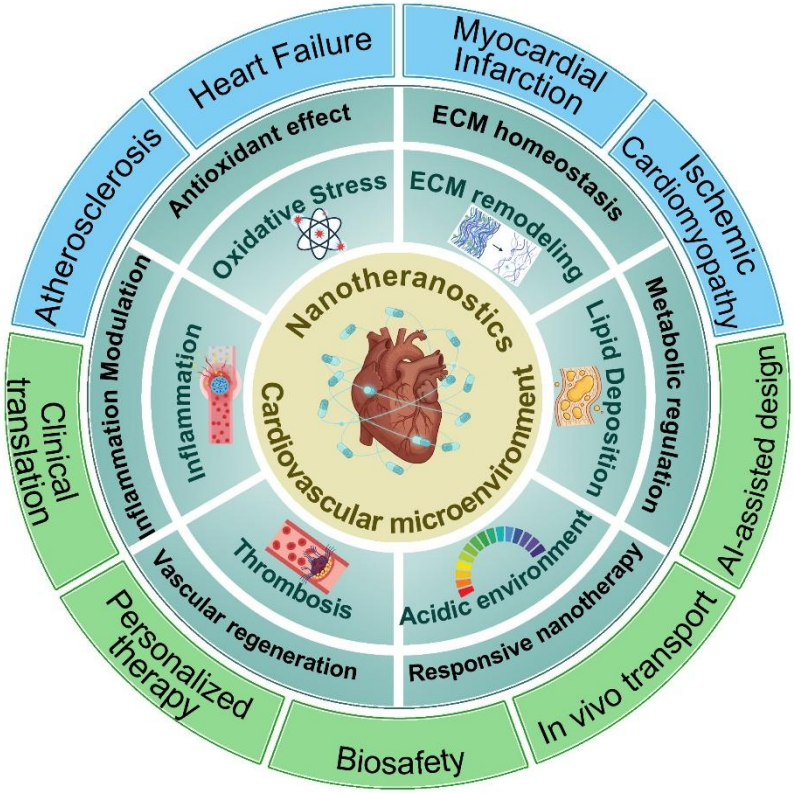


Fig. 1. Nanomedicine-mediated regulation of the pathological microenvironment for the treatment of cardiovascular diseases.

Table 1. Taxonomy of nanomedicine platforms for cardiovascular microenvironment modulation

Category	Defining feature	Representative platforms	Main therapeutic role
Nanocarrier-based systems	Nanoscale vehicles for therapeutic cargo delivery	Polymeric NPs, liposomes, micelles, nanogels	Drug/nucleic acid delivery and controlled release
Intrinsically bioactive nanomaterials	Therapeutic activity derives from intrinsic physicochemical or catalytic properties	Nanozymes, catalytic inorganic NPs	ROS regulation, catalysis, immunomodulation

Category	Defining feature	Representative platforms	Main therapeutic role
Biomimetic and hybrid nanosystems	Integration of nanomaterials with biological membranes or biomolecules	Macrophage-, platelet-, and RBC-membrane-coated NPs	Targeting, lesion homing, immune evasion
Nanoengineered biomaterial- and cell-assisted systems	Nanoscale components integrated with biomaterials or living cells	Nanocomposite hydrogels, nanoengineered MSCs	Sustained delivery, tissue repair, cellular protection

Note: These categories are defined by the predominant structural and functional characteristics of each platform, but are not mutually exclusive. Platforms that integrate multiple nanomedicine modalities may simultaneously span multiple categories.

2. Pathological Microenvironment Characteristics in Cardiovascular Diseases

CVDs constitute a major global public health burden, associated with substantial morbidity and mortality [45, 46]. The occurrence and development of these diseases are closely related to the dysregulated pathological microenvironment, which typically includes abnormal cells, molecular signals, and extracellular matrix remodeling [47]. This section systematically explores the three key characteristics of the cardiovascular microenvironment - blood vessels, myocardium, and atherosclerotic plaques. The evolution patterns and interaction mechanisms of each key characteristic at different stages of cardiovascular diseases provide a foundation for therapeutic interventions based on nanomedicine. Accurate understanding of these pathological features is crucial for regulating the mechanisms of the disease, thereby facilitating the development of more effective prevention and treatment strategies for coronary artery diseases.

The pathological vascular microenvironment consists of endothelial dysfunction, vascular wall remodeling and fibrosis, immune inflammatory infiltration, oxidative stress, and tissue acidification, which fundamentally drives the progression of CVDs. The endothelial barrier can be disrupted by hemodynamic disorders and inflammatory stimuli, thereby triggering the transformation of smooth muscle cells and the deposition of the extracellular matrix. At the same time, a positive feedback loop can be created by excessive reactive oxygen species (ROS) and pro-inflammatory cascades. All these things together make up a complicated set of processes that cause the disease to keep getting worse.

The pathological microenvironment of the myocardium undergoes continuous changes during the process of ischemia-reperfusion injury as the disease progresses. Myocardial cell necrosis is caused by excessive ROS, which is caused by acute hypoxia and reperfusion. The release of related damage molecules is triggered by this, and an inflammatory cascade reaction is promptly triggered as a result. As the healing process progresses, there is a shift in the microenvironment from acute inflammation to a repair stage with fibroblast activation and matrix deposition as characteristics. However, deterioration of cardiac function can be triggered by persistent inflammation, oxidative stress, and ECM infiltration, ultimately leading to pathological fibrosis and adverse ventricular remodeling.

The pathological microenvironment of atherosclerosis comprises lipid deposition, chronic inflammation, oxidative stress, and matrix degradation. Subendothelial lipid deposition can promote the formation of foam cells, thereby triggering an inflammatory response involving ROS and macrophage infiltration. Matrix metalloproteinase-mediated degradation dilutes the fibrous cap and expands the necrotic core, causing plaque instability. Ultimately, plaque rupture activates platelet and coagulation cascade reactions, triggering acute cardiovascular events.

3. Disease-Oriented Applications of Nanomedicine in Cardiovascular Microenvironments

This section explores the representative applications of nanomedicine in the treatment of various cardiovascular diseases, including vascular injury, myocardial injury and repair, and atherosclerosis. The discussion does not provide a detailed classification of the therapeutic mechanisms, but rather emphasizes the pathological obstacles of specific diseases, treatment goals, and representative theranostic applications (**Table 2**). These studies demonstrate how nanomedicine design can adapt to the anatomical, cellular characteristics of different cardiovascular lesions. The fourth section critically assesses the cross-disciplinary design principles, comparative performance and translational limitations of these platforms.

Table 2. Summary of Representative Nanomedicine-Based Therapeutic Interventions Targeting Cardiovascular Pathological Microenvironments

Nanoplatform	Targeting/response strategy	Therapeutic mechanism	Theranostic application	Ref.
Bio-liposome	Endothelial/macrophage dual targeting	Restores endothelial function, and promotes cholesterol efflux	Endothelial protection and synergistic anti-atherosclerosis therapy	[53]
B-NPs@MM	Macrophage membrane + ultrasound	Suppresses inflammation and promotes vascular regeneration	Macrophage-targeted anti-inflammatory therapy and vascular regeneration	[54]

Polymeric micelles	CCR2 targeting	Reverses VSMC phenotypic transition	VSMC phenotypic reprogramming and anti-atherosclerotic therapy	[60]
ECM-like HA hydrogel incorporating RepSox-loaded PEG-PLGA nanoparticles	Localized delivery with stage-specific and sustained drug release	Promotes cell proliferation, migration and angiogenesis while inhibiting TGF-β signaling and cardiac fibroblast proliferation to attenuate adverse remodeling	Localized and sustained RepSox delivery for myocardial infarction repair and anti-fibrotic therapy	[61]
FCPH	Targeted cholesterol crystal dissolution and enhanced lymphatic drainage	Dissolves cholesterol crystals, suppresses macrophage–neutrophil inflammatory crosstalk and NETs formation, enhances lymphatic drainage, and promotes cholesterol	Cholesterol crystal dissolution and lymphatic drainage enhancement for inflammation regression and anti-atherosclerosis therapy	[77]

		metabolism and immune homeostasis		
Bio-activatable human serum albumin nano-shuttle	Monocyte-mediated plaque targeting and legumain-responsive drug release	Mimics efferocytosis for selective uptake by inflammatory monocytes, co-migrates to plaques, and releases curcumin in response to legumain generated during monocyte-to-foamy macrophage differentiation	Monocyte-mediated targeted curcumin delivery and legumain-responsive anti-atherosclerosis therapy	[78]
MSeNP	Mannose receptor-mediated macrophage/plaque targeting	Inhibits calpain-mediated cleavage of ABCA1/ABCG1, improves cholesterol efflux, reduces plaque formation, and modulates	Macrophage-targeted calpain inhibition and anti-atherosclerosis therapy	[79]

		the M1/M2 macrophage ratio		
Rapa@TLNVs	M2 macrophage membrane-mediated inflammatory targeting + ROS-responsive thioketal (TK) linker	Targets inflammatory plaques, releases Rapa in response to elevated ROS, suppresses inflammation and macrophage proliferation, and reduces foam cell formation	ROS-responsive rapamycin delivery for anti-inflammatory therapy and plaque stabilization	[88]
t-PBA&NO NP	Collagen IV homing peptide-mediated vascular injury targeting + ROS-responsive release	Scavenges excessive ROS and releases ECA in response to ROS, alleviating oxidative stress and enhancing NO-mediated vascular modulation while preventing harmful RNS formation	ROS-responsive NO delivery for re-endothelialization and inhibition of neointimal formation	[89]
ROS-responsive and size-	CD44-mediated plaque targeting + ROS-	ROS-triggered size reduction	ROS-responsive deep plaque penetration and	[90]

reducible HA-Fc/NP3ST nanoassemblies	responsive disassembly and size reduction	enhances plaque penetration and macrophage-targeted cholesterol efflux	macrophage-targeted cholesterol efflux for anti-atherosclerosis therapy	
pH-sensitive fibronectin (FN) nanogels (FNC)	RGD–integrin-mediated plaque targeting + acid-responsive Schiff-base cleavage + UTMD	Acid-responsive Cur release combined with UTMD enhances antioxidant and anti-inflammatory effects to suppress plaque progression	pH-responsive curcumin delivery and ultrasound-enhanced anti-inflammatory/antioxidant therapy for atherosclerosis	[99]
ST/NCP-PEG	Plaque accumulation + acidic pH-responsive degradation and release	Acid-responsive release of ST reduces oxidative stress and promotes M2/M1 macrophage polarization	MRI-guided plaque visualization and pH-responsive simvastatin delivery for anti-atherosclerosis therapy	[100]
MeOTTI-PMEA NPs	Lipid droplet-specific fluorescence + pH-responsive probe release	Acid-responsive probe release enables efficient lipid droplet imaging in	pH-responsive lipid droplet-specific fluorescence imaging for atherosclerotic plaque visualization	[101]

		atherosclerotic plaques		
tn-MSCs	MSC-mediated delivery and ROS-responsive cytoprotection	Attenuates oxidative stress and inflammation, inhibits cardiomyocyte apoptosis, and enhances angiogenesis and cardiac repair	Antioxidant and anti-inflammatory MSC therapy for myocardial ischemia-reperfusion injury and cardiac repair	[114]
E-MSCs	MSC-mediated myocardial targeting + nanozyme-based ROS scavenging + MRI tracking	SOD-mimetic ROS scavenging alleviates oxidative stress and inflammation while enhancing MSC viability, migration and homing	MRI-tracked antioxidant stem cell therapy for myocardial infarction repair	[115]
siTTENPs	S2P peptide-mediated lesional macrophage targeting + β-cyclodextrin-mediated cholesterol clearance	Reduces oxLDL uptake and inflammation while promoting cholesterol efflux to restore lipid homeostasis	Lesional macrophage-targeted cholesterol homeostasis regulation for anti-atherosclerosis therapy	[132]

DPTP NRs	ROS scavenging by Pt–Ce nanozyme + P2Y12-mediated antiplatelet activity	Scavenges ROS to reduce oxLDL and foam cell formation while inhibiting P2Y12-mediated platelet aggregation	Synergistic foam cell inhibition and antiplatelet therapy for preventing atherosclerosis progression	[133]
Gd-MCNs/Pt-RAPA-AC	Anti-CD36-mediated macrophage targeting + H_2O_2-driven self-propulsion + NIR-triggered photothermal propulsion	H_2O_2/NIR-driven propulsion enhances plaque penetration, while photothermal ablation, anti-inflammatory activity and autophagy promotion suppress macrophage-mediated plaque progression	Dual-mode nanomotor-enhanced photothermal ablation, anti-inflammatory and pro-autophagy therapy for atherosclerosis	[148]
37pA-PtLNP/37pA-LNP/6877002	37pA-mediated macrophage targeting + ROS scavenging + TRAF6 signaling inhibition	Synergistic ROS scavenging and TRAF6 inhibition suppress M1	Macrophage-targeted ROS scavenging and inflammatory signaling inhibition for	[149]

		macrophage polarization and chronic inflammation to stabilize atherosclerotic plaques.	atherosclerotic plaque stabilization.	
Col@HMnO_2-MM	Macrophage membrane-mediated immune evasion and inflammatory plaque targeting + H_2O_2-responsive O_2 generation	Scavenges ROS and generates O_2 to alleviate oxidative stress and hypoxia, downregulate HIF-1α, enhance cholesterol efflux, and inhibit foam cell formation.	Macrophage-targeted ROS scavenging and hypoxia relief for enhanced cholesterol efflux and anti-atherosclerosis therapy.	[150]
FPD@CD	Dextran sulfate - mediated macrophage targeting + LIFU-triggered acoustic droplet vaporization	LIFU-triggered acoustic droplet vaporization induces targeted macrophage apoptosis, thereby shrinking vulnerable plaques and	NIRF/MRI-guided macrophage-targeted ablation of vulnerable plaques for plaque stabilization.	[167]

		reducing vascular stenosis.		
HMTL@PM	Thrombus targeting + weakly acidic microenvironment-responsive dissociation	Alleviates inflammation, promotes thrombolysis and anticoagulation, and enhances cholesterol efflux.	Thrombus-targeted and microenvironment-responsive therapy for thrombolysis and atherosclerosis management	[181]
UCATS-UK	Thrombus targeting + NIR-triggered controlled release	Synergistic thrombolysis and anticoagulation through controlled UK and NO release.	Fluorescence-guided thrombus-targeted thrombolysis and anticoagulation therapy	[182]
Clot-targeted self-regulated nanoscale polymeric gel	Clot targeting + thrombin-responsive closed-loop release	Thrombin-responsive hirudin release enhances anticoagulation while reducing adverse effects.	Thrombus-targeted and thrombin-responsive anticoagulant therapy for preventing and inhibiting thrombosis	[183]

Note: B-NPs@MM: Biomimetic Nanoparticles coated with Macrophage Membranes; FCPH: Ferulic acid-loaded β-cyclodextrin Polymer coated with Polydopamine and Hyaluronic acid; MSeNP: D-mannose-modified selenium nanoparticles; Rapa@TLNVs: Rapamycin-loaded Thioketal-linked Lipid/M2 macrophage-derived Nanovesicles; t-PBA&NO NP: ROS-responsive NO nanomedicine (t-PBA&NO NP)

with ROS scavenging ability; FNC: pH-sensitive fibronectin (FN) nanogels (FNC); ST/NCP-PEG: Simvastatin-loaded PEGylated Nanoscale Coordination Polymer nanoparticles; MeOTTI-PMEA NPs: MeOTTI-loaded PMEA nanoparticles; tn-MSCs: TPCD NP-internalized mesenchymal stem cells; E-MSCs: Mn_3O_4@PDA nanozyme-engineered mesenchymal stem cells; siTTENPs: siTRPM2-targeted and efflux-enhanced nanoparticles; DPTP NRs: PEGylated Pt-Ce bimetallic nanostructures; Gd-MCNs/Pt-RAPA-AC: Gd-doped mesoporous carbon nanoparticles/Pt with rapamycin (RAPA) loading and AntiCD36 modification; 37pA-PtLNP/37pA-LNP/6877002: 37pA peptide embedded-Pt lipid nanoparticles/tumor necrosis factor-associated factor 6 (TRAF6) inhibitor (6877002)-loaded poly(ε-caprolactone)-b-polyethylene glycol-b-poly(ε-caprolactone) (PCEC); Col@HMMnO_2-MM: macrophage membrane-functionalized hollow mesoporous manganese dioxide nanomedicine; FPD@CD: Fe_3O_4-PFH-DiR@CS-DS nanoparticles; HMTL@PM: Platelet membrane-coated Hirudin/Mn^{2+}/Tannic acid/Lumbrokinase nanoparticles; UCATS-UK: Upconversion nanoparticle-regulated Antithrombotic System - urokinase.

3.1 Nanomedicine-Based Interventions Targeting the Vascular Microenvironment

3.1.1 Nanomedicine-Based Interventions for Endothelial Injury and Dysfunction

Endothelial cells constitute a dynamic cellular barrier at the luminal surface of blood vessels and function as essential regulators of vascular homeostasis, orchestrating bidirectional communication between the bloodstream and vascular wall [48, 49]. In CVDs, endothelial injury and dysfunction represent early and central pathogenic events that initiate and sustain maladaptive remodeling of the vascular microenvironment [50-52]. This section systematically examines the molecular and cellular mechanisms underlying endothelial barrier disruption and functional impairment, with emphasis on their contribution to the establishment of a pro-inflammatory, pro-thrombotic, and pro-atherogenic phenotype.

Understanding these early pathological alterations is essential for nanomedicine-based therapeutic intervention, as rationally engineered delivery systems can be designed to selectively restore endothelial homeostasis or deliver therapeutic agents to injured endothelial cells with high spatial and functional precision. For example, Zhang *et al.* developed a dual-targeting bio-liposomal nanotherapeutic HA-ML@ES to ameliorate endothelial dysfunction in early-stage atherosclerosis (**Fig. 2A**) [53]. Co-encapsulating shikonin and evolocumab, the nanocarrier was demonstrated to concurrently target dysfunctional endothelial cells and pro-inflammatory macrophages. Both *in vitro* and *in vivo* experiments demonstrated that this nanotherapy effectively ameliorated endothelial dysfunction by suppressing aberrant glycolytic flux while simultaneously restoring macrophage cholesterol efflux capacity. These synergistic effects collectively attenuated atherosclerotic plaque progression, establishing a dual-cell-targeted therapeutic strategy (**Fig. 2B–D**). This study demonstrates the potential of dual-cell targeting in modulating endothelial cell-macrophage interactions in atherosclerosis. HA-ML@ES simultaneously targets dysfunctional endothelial cells and inflammatory macrophages *via* hyaluronic acid-CD44 binding, exhibiting enhanced plaque accumulation and therapeutic efficacy in $ApoE^{-/-}$ mice.

Another strategy is to deliver gas molecules, particularly nitric oxide (NO), a critical regulator of vascular homeostasis. For instance, Xu *et al.* designed a biomimetic nanoparticle derived from macrophage membranes containing a poly(lactic-co-glycolic acid) and an ultrasound-sensitive NO donor to deliver NO gas-based therapy for achieving atherosclerotic gas-based therapy (**Fig. 2E**) [54]. This biomimetic nanoparticle mimicked the biological characteristics of physiological macrophages and could actively target inflammatory atherosclerotic plaques and avoid immune surveillance. Additionally, this design released NO on demand at the disease site through local ultrasound activation (**Fig. 2F, G**). Experimental results demonstrated that this platform significantly promoted endothelial regeneration, reduced local inflammation, and inhibited neointimal hyperplasia. In summary, this study proposes a

stimulus-responsive nanoplatform that combines biomimetic design with ultrasound activation to achieve precise drug delivery through gaseous carriers. This ultrasound-responsive biomimetic system can achieve targeted microenvironmental regulation within atherosclerosis, promoting on-demand treatment of blood vessels.

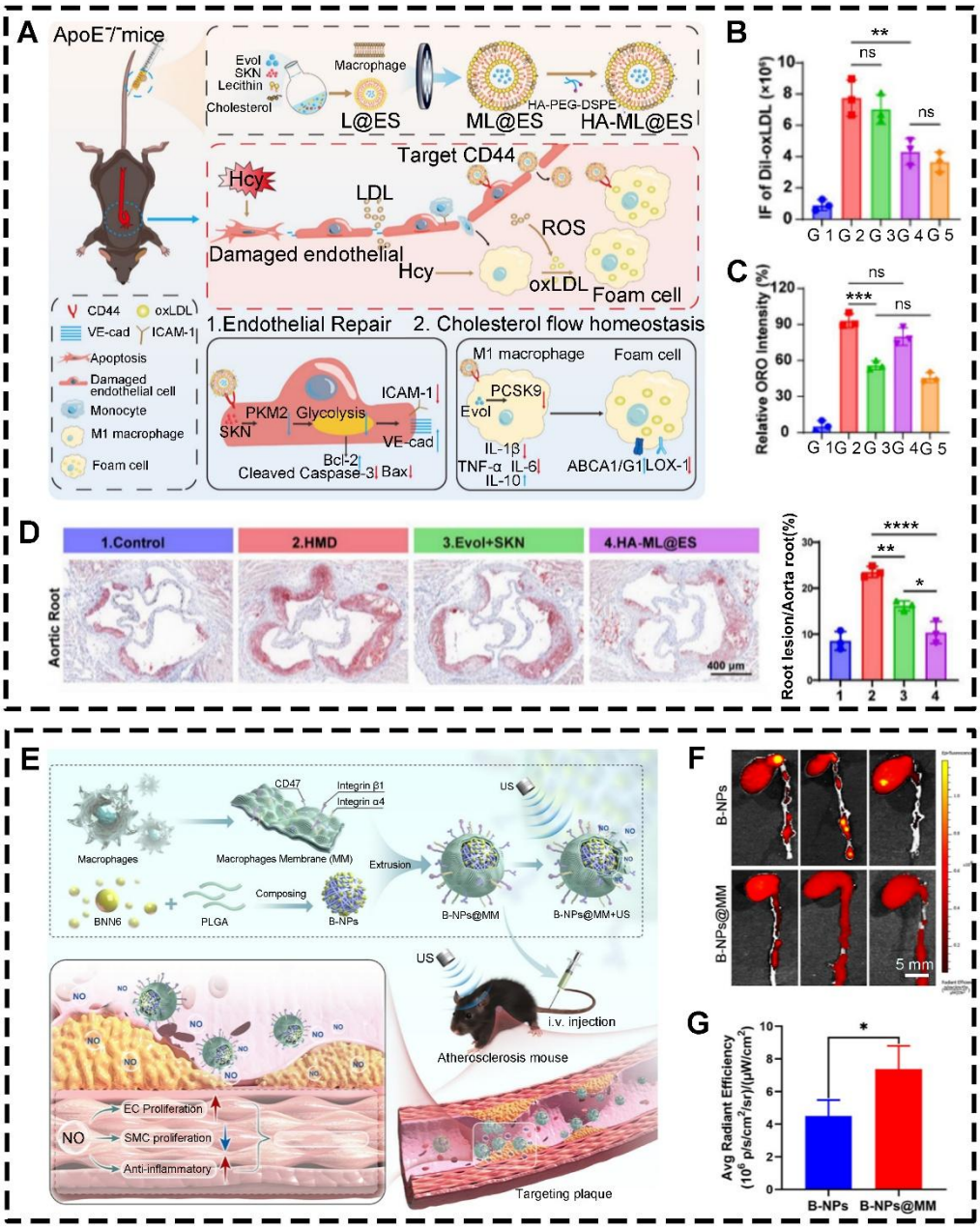


Fig. 2. (A) Schematic illustration of the preparation of HA-ML@ES nanoparticles and their therapeutic strategy for atherosclerosis. (B) Quantification of Dil-oxLDL uptake in RAW264.7 cells following different treatments. (C) Representative Oil Red O (ORO) staining and quantitative analysis of RAW264.7 cells following different

treatments. (D) Evaluation and quantification of atherosclerotic lesion areas based on ORO staining among the indicated groups. (E) Schematic illustration of the structure of B-NPs@MM and its therapeutic mechanism against atherosclerosis. (F) *Ex vivo* fluorescence imaging of excised cardiovascular tissues at 24 h after systemic administration of DIR-labeled nanoparticles. (G) Quantitative analysis of the fluorescence signals shown in (F). (A-D) Reproduced with permission [53]. Copyright 2025, Springer Nature. (E-G) Reproduced with permission [54]. Copyright 2025, Elsevier.

3.1.2 Nanomedicine-Based Interventions for Vascular Remodeling and Fibrosis

In addition to initial endothelial dysfunction, the vascular microenvironment of CVDs undergoes substantial structural and functional remodeling, commonly termed vascular remodeling and fibrosis [55-56]. In healthy blood vessels, vascular smooth muscle cells (VSMCs) mainly express contraction markers such as α-SMA, SM22α and MYH11, which maintain vascular tension and structural integrity. However, the expression of contractile proteins in VSMCs is downregulated under pathological stimuli, while they proliferate and migrate, thereby promoting vascular remodeling and fibrosis. These changes collectively lead to vascular hardening, a narrowed lumen and decreased hemodynamic function [57–59]. Importantly, these biological alterations in the microenvironment reflect the severity of the disease and limit the effectiveness of traditional treatments.

To precisely regulate this complex pathological process, nanomedicine provides researchers with an effective strategy. For example, Chin *et al.* developed polymer microspheres that targeted CCR2 to deliver miR-145 and reverse plaques for treating cardiovascular diseases (Fig. 3A) [60]. Specifically, these polymers delivered small RNAs into smooth muscle cells, thereby promoting phenotypic transformation and inhibiting pro-inflammatory genes. In early and mid-stage $ApoE^{-/-}$ mouse models of atherosclerosis, miR-145-loaded microspheres enhanced collagen deposition within the

lesions, improved the thickness and integrity of the fibrous cap, and overall alleviated vascular remodeling and fibrosis (**Fig. 3B–D**). These research results indicate that nanocarrier-mediated miRNA delivery restores vascular homeostasis, providing an advanced therapeutic strategy for vascular dysfunction in cardiovascular diseases.

In a complementary strategy targeting the complex post-myocardial infarction (MI) cardiac microenvironment, Wang *et al.* developed a rationally designed, dual-functional therapeutic platform [61]. Specifically, they engineered an injectable hydrogel mimicking the native ECM, tailored to intervene sequentially across distinct pathological phases of cardiac repair. This dual-component platform delivered temporally phased therapeutic interventions at the nanoscale. During the acute phase, hydrogel-conjugated bioactive peptides promoted angiogenesis and cardiomyocyte migration to counteract ischemic injury and apoptosis (**Fig. 3E, F**). Subsequently, RepSox-loaded PLGA nanoparticles uniformly dispersed in the matrix provide weeks-long sustained release, specifically targeting maladaptive fibrosis throughout the subacute and chronic phases (**Fig. 3G**). In a rat MI model, treatment with this composite hydrogel significantly reduced interstitial fibrosis, preserved left ventricular wall thickness, and enhanced systolic and diastolic function. This study demonstrates the potential of a programmable hydrogel platform to sequentially address different stages of myocardial infarction repair. The platform synergistically promotes myocardial regeneration while suppressing fibrotic remodeling by sequentially releasing bioactive peptides and RepSox nanoparticles.

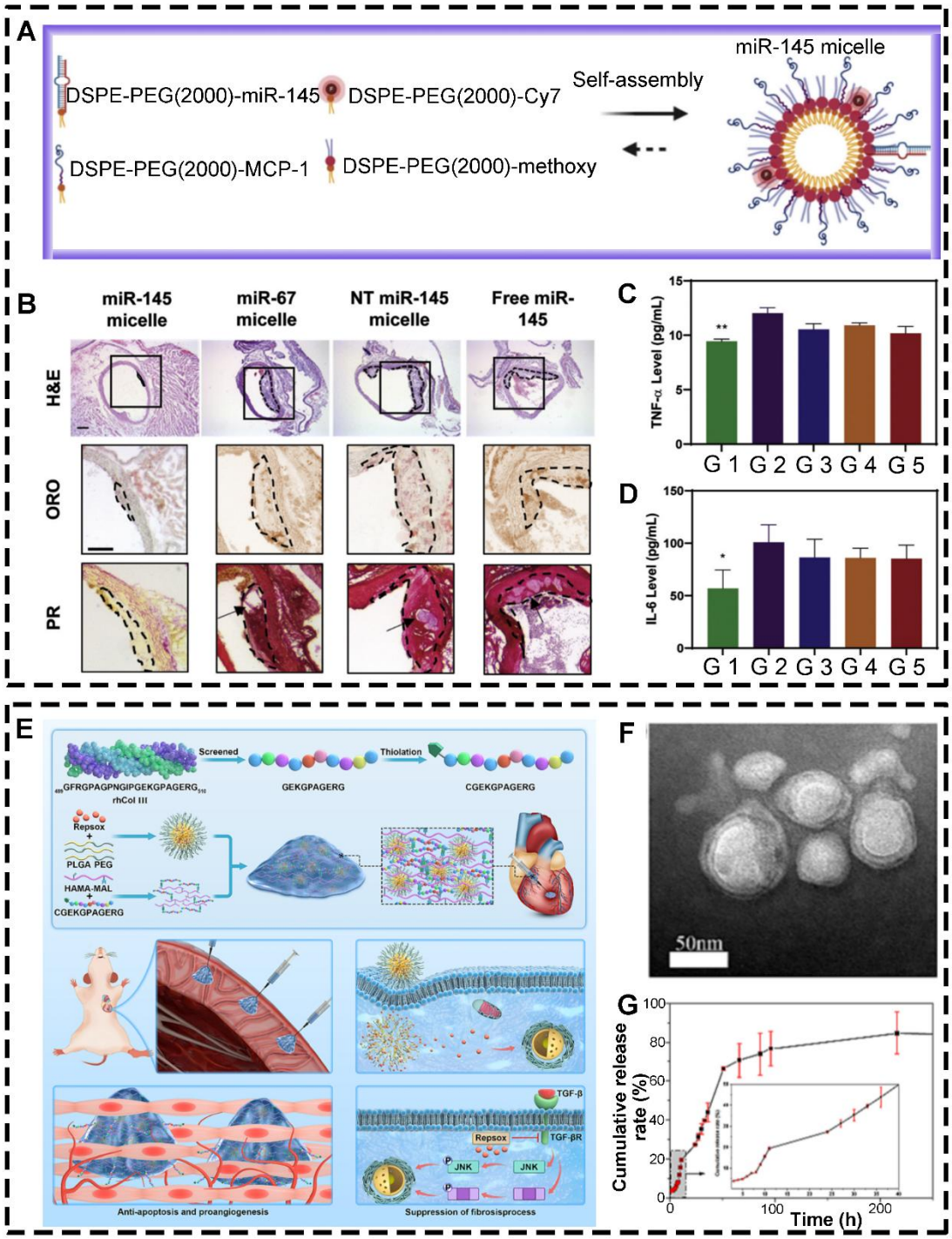


Fig. 3. (A) Schematic representation of the self-assembly process and multifunctional properties of miR-145 micelles. (B) Representative sections of the ascending aorta stained with hematoxylin and eosin (H&E), Oil Red O (ORO), and picrosirius red (PR). (C) Serum TNF-α levels in ApoE$^{-/-}$ mice at the early-stage following treatment with miR-145 micelles. (D) Serum interleukin-6 (IL-6) levels in ApoE$^{-/-}$ mice at the early-stage following treatment with miR-145 micelles. (E) Schematic illustration of the

preparation of composite hydrogels for myocardial infarction therapy and their drug release mechanism. (F) Representative transmission electron microscopy (TEM) images of Repsox NPs. (G) Cumulative in vitro release of Repsox from the composite hydrogel. (A-D) Reproduced with permission [60]. Copyright 2021, Elsevier. (E-G) Reproduced with permission [61]. Copyright 2023, Elsevier.

3.1.3 Nanomedicine-Based Interventions Targeting Inflammatory and Immune Cell Infiltration

While healthy vasculature sustains immune homeostasis, CVD provokes a pro-inflammatory microenvironmental shift characterized by chronic immune cell recruitment and activation [62-65]. Monocytes, macrophages, T lymphocytes, and neutrophils represent the principal immune effector cells recruited to diseased vessels. Their dynamic interactions within the local vascular microenvironment drive the initiation, progression, and complications of vascular diseases including atherosclerosis, hypertension, and in-stent restenosis [66–69]. Upon activation, these cells release a spectrum of pro-inflammatory mediators including TNF-α, IL-1β, monocyte chemoattractant protein-1 (MCP-1), and ROS. Inflammatory mediators induce the phenotypic transformation of VSMCs and lead to the degradation of extracellular matrix, thereby exacerbating the vulnerability of atherosclerotic plaques [70–72]. Therefore, targeting the regulation of inflammatory-related mechanisms has become a pivotal therapeutic strategy for CVDs [73-76].

For instance, a study by Peng *et al.* introduced a pH-responsive targeted nanosystem (FCPH) composed of cyclodextrin polymers and fumaric acid, which employed a novel "internal-external combination" approach to reshape the inflammatory microenvironment for the treatment of atherosclerosis (**Fig. 4A**) [77]. This nanosystem first bound to the CD44 receptor through hyaluronic acid, targeting macrophages in the plaque. The acidic plaque environment triggered the response and release of the loaded two drugs by the nanosystem. The cyclodextrin polymer could dissolve the cholesterol

crystals that trigger inflammation; and fumaric acid could restore the impaired lymphatic drainage function. This dual mechanism not only eliminated the key triggers of inflammation but also enhanced the clearance of lipids and inflammatory molecules in the blood vessels. The results showed that the pro-inflammatory M1 macrophages and neutrophils within the plaque were significantly reduced, the levels of inflammatory factors decreased, and the development of atherosclerosis was significantly inhibited in the animal model (**Fig. 4B, C**). FCPH could promote the clearance of cholesterol crystals and inhibited the inflammatory response of macrophages, thereby significantly reducing the plaque burden in ApoE$^{-/-}$ mice. This study also targets cholesterol deposition and lymphatic system dysfunction, indicating that this platform has the potential to regulate the atherosclerotic microenvironment.

Further advancing this concept of intelligent microenvironment modulation, Fu *et al.* developed a "differentiation-surveilling" nano-shuttle that hijacked the disease process itself for targeted therapy (**Fig. 4D**) [78]. Their approach utilized inflammatory monocytes, the very cells that drove plaque formation, as "Trojan horses". The nano-shuttle was modified with phosphatidylserine to simulate the surface of apoptotic cells, thereby inducing monocytes to specifically phagocytose these nanoparticles. The monocytes carrying the nanocarrier drugs then naturally migrated to the atherosclerotic plaques. When the monocytes differentiated into pro-inflammatory foam macrophages within the plaques, the expression of the enzyme legumain was significantly upregulated. Legumain was specifically cleaved by the conformation-specific cutting of the nano-shuttle, thereby releasing the therapeutic drug curcumin. In animal models, this strategy significantly reduced plaque inflammation and delayed the progression of atherosclerosis. This study combines targeted lesion targeting and responsive drug release, precisely regulating the pathological microenvironment of the cardiovascular system through targeted delivery and controlled activation.

In addition to the responsive drug release strategy, Yang *et al.* designed selenium nanoparticles (SeNPs) with anti-inflammatory properties to target macrophages directly

for treating CVDs (**Fig. 4E, F**) [79]. The surface of these nanoparticles was coated with a mannan layer to target plaque macrophages and contained an added calpain inhibitor peptide (**Fig. 4G**). By specifically targeting macrophages and inhibiting their intracellular calcium protease activity, the MSeNP@CIP nanomedicine reprogrammed macrophages from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype. This strategy demonstrates microenvironmental regulation and plays an active therapeutic role by targeting enzymes related to the disease. In addition to directly targeting macrophages in the lesion site, the nanomedicine can also utilize monocytes as an endogenous carrier to achieve specific enrichment of the drug at the lesion site. To avoid the EPR effect of vascular endothelium and complex *in vitro* cell operations, Liu *et al.* developed an "in vivo drug depot" (DSS/PB@BSP) using monocytes as the carrier for the treatment of myocardial ischemia-reperfusion injury [80]. The surface DSS could enable the nanoparticles to bind to the clearance receptors on circulating monocytes, achieving EPR-independent enrichment of the damaged myocardium after intravenous injection. The hollow Prussian blue nanozyme could eliminate ROS, while the encapsulated betamethasone could reprogram monocytes into anti-inflammatory M2-type macrophages, providing an alternative to traditional cell therapy.

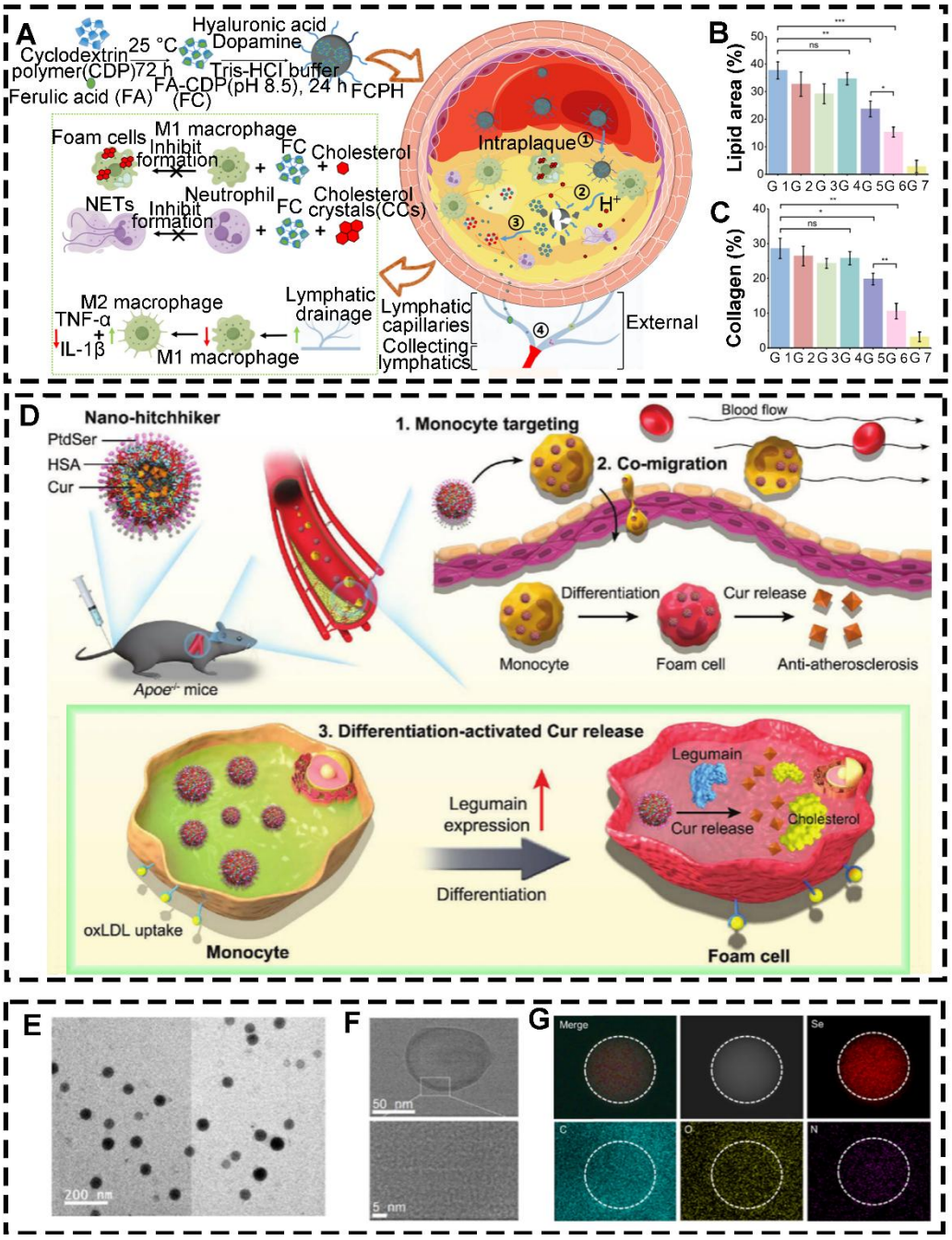


Fig. 4. (A) Schematic illustration of the preparation process and therapeutic mechanism of FCPH. (B) Quantification of lipid-rich areas in aortic sections. (C) Quantification of collagen-positive areas in aortic sections. (D) Schematic illustration of differentiation-monitoring nanocarriers targeting atherosclerotic plaques and promoting macrophage functional reprogramming. (E) Representative transmission electron microscopy (TEM) images of MSeNP@CIP. (F) Representative high-resolution transmission electron microscopy (HRTEM) images of MSeNP@CIP. (G) Elemental mapping of MSeNP@CIP nanocomposites. (A-C) Reproduced with permission [77]. Copyright

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3.1.4 Nanomedicine-Based Interventions for Oxidative Stress

Within the pathological vascular microenvironment of cardiovascular diseases, oxidative stress constitutes a pervasive and pathophysiologically consequential driver of disease progression [81]. It arises from a sustained imbalance between ROS generation and endogenous antioxidant defense capacity, resulting in cumulative macromolecular damage, chronic low-grade inflammation, and disruption of redox-sensitive signaling pathways essential for vascular homeostasis [82-84]. Enhanced oxidative stress can promote the phenotypic changes and excessive proliferation of VSMCs, and exacerbate the secretion of pro-inflammatory cytokines. At the same time, oxidative stress can also catalyze the oxidation of low-density lipoprotein (LDL), synergistically promoting the formation and progression of atherosclerotic lesions [85-87]. Given its crucial role in the pathological process of CVDs, targeted inhibition of oxidative stress has become a favorable therapeutic strategy in cardiovascular medicine.

For instance, Zhou and his colleagues developed an innovative ROS-responsive bionic hybrid vesicle Rapa@TLNVs to enhance targeting of the atherosclerotic plaque microenvironment for the treatment of atherosclerosis (**Fig. 5A**) [88]. These nanovesicles were formed by the fusion of the anti-inflammatory M2 macrophage membrane with a lipid membrane containing ROS-sensitive thioester bonds (TK), and the therapeutic drug rapamycin was loaded within them. This design cleverly exploited the pathological features of atherosclerosis in two ways. First, the M2 macrophage membrane provided a natural "inflammatory tropism," promoting nanovesicle accumulation at inflammatory plaque lesions (**Fig. 5B**). Subsequently, excessive ROS in the lesion area led to the breakage of the TK connection region, thereby achieving the responsive release of rapamycin. The released rapamycin was a known autophagy inducer, which could reduce the formation of foam cells and inhibit the proliferation of

macrophages. In preclinical studies using ApoE$^{-/-}$ mice, a common model for atherosclerosis, administration of Rapa@TLNVs led to significant therapeutic benefits, including a reduction in the inflammatory response, decreased lipid deposition, and enhanced plaque stability (**Fig. 5C**). The nanovesicles exhibited a significant enhancement in fluorescence signal in the aorta of mice with atherosclerosis, their co-localization with plaque macrophages was detected in the experiment. However, the biodistribution analysis indicated that these nanovesicles mainly accumulated in the liver and spleen. The absolute plaque delivery efficiency could not be quantitatively determined due to the lack of reported percentage of injection dose per gram of tissue (%ID/g), rendering it difficult to accurately assess the specific off-target distribution. This strategy, which combines biomimetic targeting of the immune microenvironment with a smart, ROS-responsive drug release mechanism, represents a promising and sophisticated approach for the treatment of atherosclerosis and other inflammatory diseases.

In a complementary approach, Li and colleagues addressed a different challenge: the paradox where the therapeutic gasotransmitter NO, crucial for vascular health, was rapidly consumed by ROS at injury sites, forming damaging peroxynitrite ($ONOO^-$) and limiting its efficacy (**Fig. 5D**) [89]. To overcome this, they engineered a ROS-responsive nanomedicine (t-PBA&NO NP) that executed a synergistic, two-stage therapeutic action. This nanoparticle was built on a cyclodextrin-based scaffold and co-delivered an NO donor and a ROS-scavenging agent, ethyl caffeate (ECA), the latter being masked by a ROS-cleavable boronic ester linker. Upon reaching the high-ROS environment of a vascular injury, the nanoparticle first responded by breaking the linker to release ECA, which potently scavenged local ROS. This initial ROS depletion created a more permissive microenvironment, protecting the co-delivered NO from degradation. The preserved, now highly bioavailable NO could then effectively carry out its functions, such as promoting faster re-endothelialization and inhibiting the neointimal formation that led to restenosis. In this strategy, one component regulated

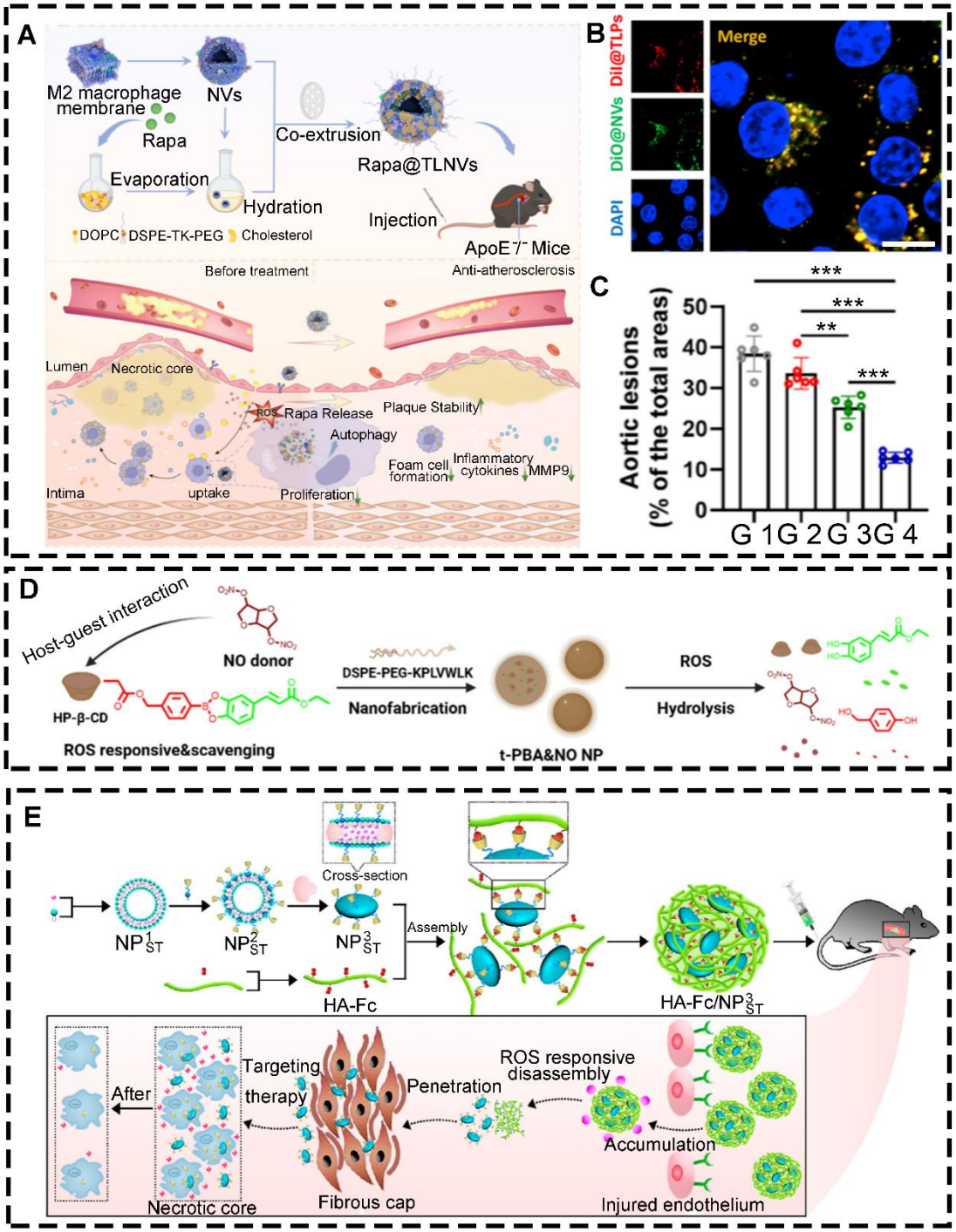


Fig. 5. (A) Schematic illustration of the mechanism of ROS-responsive biomimetic hybrid vesicles RAPA@TLNVs for the treatment of atherosclerosis in an inflammatory microenvironment. (B) Confocal laser scanning microscopy images showing the cellular uptake of fluorescently labeled TLNVs. (C) Quantification of aortic lesion area. (D) Schematic illustration of the synthesis of ROS-responsive and ROS-scavenging nanomedicines for the treatment of vascular injury-related diseases. (E) Schematic

illustration of the assembly of ROS-responsive, size-tunable HA-FC/NP3ST nanocomponents and their proposed *in vivo* therapeutic behavior. (A-C) Reproduced with permission [88]. Copyright 2024, Elsevier. (D) Reproduced with permission [89]. Copyright 2024, KeAi Publishing. (E) Reproduced with permission [90]. Copyright 2023, KeAi Publishing.

the pathological microenvironment, while the other component provided complementary therapeutic effects. This provides an innovative CVDs treatment strategy that regulates the pathological mechanisms related to oxidative stress and endothelial dysfunction.

Meanwhile, He and colleagues constructed a ROS responsive nano-assembling HA-Fc/NP3_ST comprising ferrocene-modified hyaluronic acid (HA-Fc) and β-cyclodextrin (β-CD) for targeted treatment of atherosclerosis (**Fig. 5E**) [90]. This study adopted an innovative strategy, regarding ROS not merely as a pathological product but as a molecular switch that drove the precise drug release of the nano-carriers. In the blood, HA-Fc/NP3_ST achieved local aggregation at the lesion site due to the abundant CD44 receptor on the surface of damaged endothelial cells. Upon entering the plaque intima, the pathologically elevated ROS concentration promoted oxidation of ferrocene to hydrophilic ferrocenium (Fc^+), triggering disintegration of the host-guest cross-linking and in situ release of the ultra-small NP^3_ST cores. These small-sized NP^3_ST particles could then penetrate the dense fibrous cap to reach the plaque core, where they specifically targeted foam macrophages and synergistically induced macrophage polarization toward the anti-inflammatory M2 phenotype, significantly suppressing inflammatory cytokine release. In the $ApoE^{-/-}$ atherosclerosis mouse model, HA-Fc/NP^3_ST demonstrated excellent efficacy and safety, markedly reducing plaque area and lipid deposition, substantially decreasing macrophage infiltration, and significantly ameliorating systemic inflammation. This integrated strategy, combining long circulation, receptor-mediated targeting, ROS-responsive size reduction, and deep anti-

inflammatory clearance, provides a highly promising delivery paradigm for overcoming the barriers imposed by the dense plaque microenvironment.

3.1.5 Nanomedicine-Based Interventions Targeting the Acidic Microenvironment

A frequently underappreciated yet pathophysiologically significant feature of the pathological vascular microenvironment in CVDs is localized tissue acidosis [91-92]. When the blocked microcirculation prevented the smooth excretion of acids, the local blood vessels will gradually become acidic [93-95]. This acidic environment not only aggravates vascular inflammation but also makes the blood vessel plaques more fragile and prone to rupture [96-98]. Therefore, the nanomedicine strategies aimed at addressing and improving the acidic state of blood vessels has become a promising new direction for precise treatment of CVDs.

Notably, the acidic microenvironments can be ingeniously employed as an endogenous trigger factor for the release of targeted drugs. For instance, a pH-sensitive nanogel made of fibronectin and loaded with curcumin has been developed for the treatment of atherosclerosis (**Fig. 6A**) [99]. The nanogels were connected through Schiff bonds, which could be decomposed in the acidic environment within the plaque, thereby achieving the controlled release of curcumin. The naturally existing arginine-glycine-aspartic acid (RGD) sequence on fibronectin enabled the nanogels to specifically recognize the integrins highly expressed on the surface of plaque cells, ensuring the local delivery of the drug. With potent anti-inflammatory and antioxidant properties, it helped to reduce the ROS and inflammatory factors secreted by macrophages at all stages of atherosclerosis. Additionally, this nanogel system was combined with the ultrasound-targeted microbubble disruption (UTMD) technology, which was a technique that employs ultrasound waves to destroy microbubbles formed in the intima of the plaque to create temporary channels. This increased the permeability of the plaque, promoting the deep penetration and accumulation of the nanogel within the lesion. *In vitro* and *in vivo* studies have demonstrated the effectiveness of this

combined method in inhibiting the progression of atherosclerotic plaques (**Fig. 6B and C**). This multi-target strategy utilizes the acidic microenvironment to trigger drug release, demonstrating the potential of nanomedicine to enable precise treatment.

Similarly, another strategy has been developed using pH-responsive nanoparticles for the targeted delivery of simvastatin [100]. These nanoparticles, based on nanoscale coordination polymers, were engineered to be stable at neutral pH but to disassemble within the acidic microenvironment of atherosclerotic plaques. Upon reaching the plaque, the acidic conditions triggered the release of simvastatin, which then exerted strong antioxidant and anti-inflammatory effects locally. This targeted approach had been demonstrated to reduce ROS production and increase the ratio of anti-inflammatory M2 to pro-inflammatory M1 macrophages within the plaque. Preclinical in vivo studies demonstrated that this pH-responsive nanoparticle exhibited superior therapeutic effects, which could significantly reduce the volume of plaques. Moreover, these nanoparticles also introduced MRI contrast agents (Gd^{3+}), enabling the visualization and diagnosis of plaques. In summary, this study exploits the distinctive pathological features of the cardiovascular microenvironment to effectively treat CVDs.

Furthermore, the acidic microenvironment of atherosclerosis not only can be exploited for targeted delivery, but also for advanced diagnosis. Lipid droplets accumulate abnormally in diseases such as atherosclerosis, thus enabling an important diagnostic target. Fluorescent probes usually have hydrophobic properties, which limit their solubility and make *in vivo* visualization difficult. To solve this problem, researchers developed a pH-responsive nanodiagnostic system, MeOTTI-PMEA (**Fig. 6D**) [101]. This system exploited a polymeric micelle to carry a novel fluorescent probe with aggregation-induced emission characteristics, which caused it to light up in a lipid-rich environment (**Fig. 6E**). The nanoparticles were stable in circulation at a normal physiological pH but were designed to rapidly release the imaging probe when they encountered the acidic environment within the plaque (**Fig. 6F, G**). Once released, the probe could efficiently light up the lipid droplets. The pH-responsive MeOTTI-PMEA

nanoparticles significantly enhanced AIE probe biocompatibility and exhibited fluorescence accumulation in atherosclerotic plaques. However, ex vivo imaging also revealed strong liver fluorescence, and this study did not quantify the biological distribution in plaques and major organs (expressed as %ID/g), which limited the assessment of the absolute plaque-targeting efficiency and off-target accumulation.

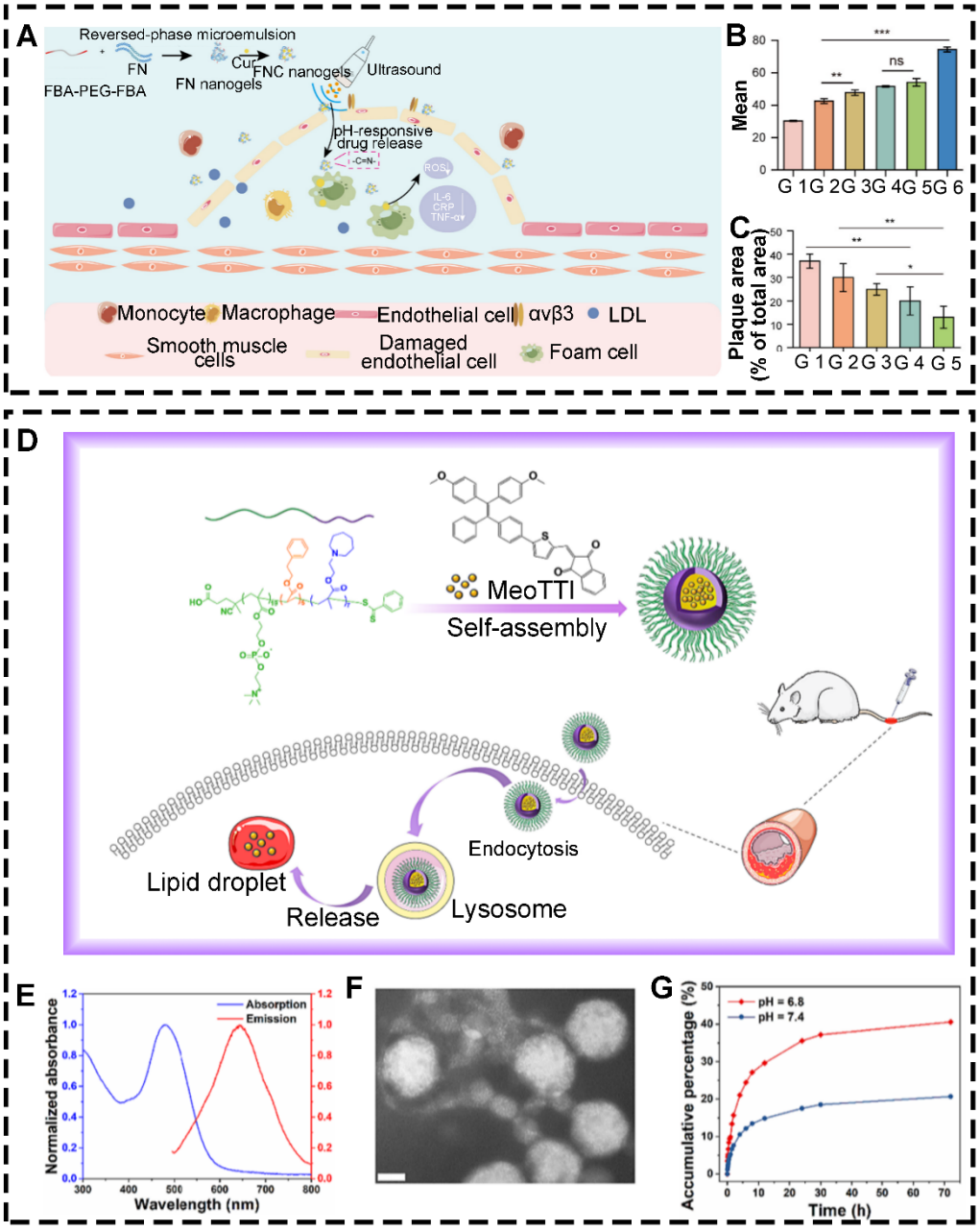


Fig. 6. (A) Schematic illustration of the synthesis strategy of pH-responsive FNC nanogels and their synergistic mechanism with UTMD for delaying atherosclerosis progression through the regulation of plaque inflammation and ROS. (B) Quantification

of intracellular ROS levels in RAW264.7 cells following different treatments, as determined by flow cytometry. (C) Quantification of the relative plaque area in aortic sinus sections. (D) Schematic illustration of LDS-specific imaging of Meotti-PMEA nanoparticles in cells and atherosclerotic plaques. (E) Normalized absorption and emission spectra of Meotti-PMEA nanoparticles in PBS. (F) Transmission electron microscopy (TEM) image of Meotti-PMEA nanoparticles at pH 6.8. (G) Cumulative release of Meotti from Meotti-PMEA nanoparticles under different pH conditions. (A-C) Reproduced with permission [99]. Copyright 2025, Elsevier. (D-G) Reproduced with permission [101]. Copyright 2023, Elsevier.

3.2 Nanomedicine-Based Interventions Targeting the Myocardial Microenvironment

3.2.1 Nanomedicine-Based Interventions for Ischemia-Reperfusion Injury and Myocardial Repair

The myocardial tissue, owing to its structural and functional fragility, is especially susceptible to damage during acute cardiovascular events. Following ischemia-reperfusion injury (IRI), a hallmark complication of myocardial infarction and subsequent revascularization, the cardiac microenvironment undergoes profound and temporally coordinated pathological alterations [102-104]. The IRI process triggers a series of complex reactions, including oxidative stress, cardiomyocyte apoptosis and necrosis, as well as vascular obstruction, which collectively lead to myocardial damage exceeding the initial ischemic injury level [105-107]. Subsequently, the microenvironment dynamically repairs itself through the proliferation and activation of fibroblasts, deposition of extracellular matrix, infiltration of immune cells, and formation of collagen-rich scars. However, it is prone to cause abnormal ventricular remodeling and ejection function impairment when its regulation becomes abnormal, and eventually progress to heart failure [108-110].

The nanoplatform can alleviate IRI by eliminating free radicals, inhibiting inflammation or protecting cardiomyocytes, thereby promoting beneficial repair processes [111-113]. For example, Pan *et al.* engineered mesenchymal stem cells (MSCs) with an anti-oxidative and anti-inflammatory nanotherapy (TPCD NP) to better withstand and remodel the hostile post-IRI microenvironment (**Fig. 7A-C**) [114]. These tn-MSCs were typically able to reduce excessive ROS after transplantation because excessive ROS could damage the survival and function of stem cells (**Fig. 7D**). Nanoparticle engineering not only protected MSCs from apoptosis but also enhanced their paracrine activity under oxidative stress conditions. The tn-MSCs protected cardiomyocytes from ROS damage partly by regulating the p53 signal, promoting endothelial cell angiogenesis. In mouse experiments, the tn-MSCs significantly prolonged the cell survival time in damaged myocardium, thereby significantly reducing the infarct area, improving cardiac function, and alleviating adverse remodeling. This study suggests that tn-MSCs may at least partially exert their effects by regulating the pathological microenvironment, substantially promoting cardiac repair.

Le *et al.* designed a multifunctional nanozyme that further integrated diagnostic functions to simultaneously improve the therapeutic microenvironment and enable real-time tracking of transplanted cells (**Fig. 7E**) [115]. They developed a nanozyme composed of a manganese oxide (Mn_3O_4) core encapsulated by polydopamine (PDA), which exhibited strong superoxide dismutase (SOD) mimicking activity. When these Mn_3O_4@PDA nanozymes were taken up by MSCs, the "engineered MSCs" (E-MSCs) significantly enhanced the protective effect against the characteristic oxidative stress of the heart after myocardial infarction. Crucially, the antioxidant properties of the nanozyme improved the microenvironment, thereby promoting the survival, migration, and paracrine functions of MSCs. Additionally, the manganese core served as an excellent T1-weighted contrast agent in *in vivo* MRI, enabling efficient disease tracking (**Fig. 7F, G**). In a mouse MI model, this dual-function strategy led to superior cardiac

repair and allowed for the successful tracking of the engineered cells homing to the site of injury, addressing two of the major bottlenecks in cardiac cell therapy.

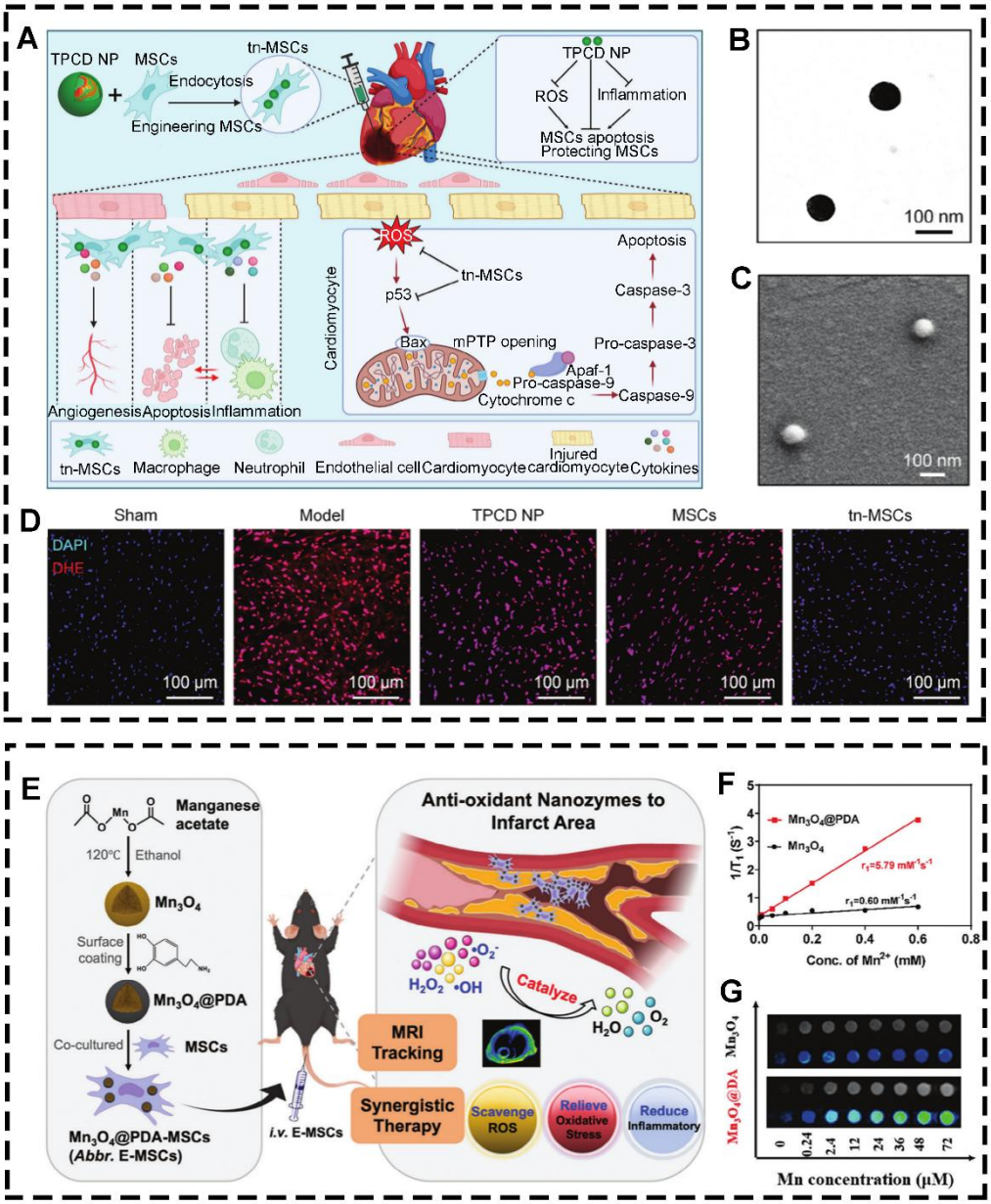


Fig. 7. (A) Schematic illustration of TPCD-NP nanotherapy for MSC-mediated repair of myocardial ischemia–reperfusion injury. (B) Transmission electron microscopy (TEM) image showing the typical morphology of TPCD-NPs. (C) Scanning electron microscopy (SEM) image showing the typical morphology of TPCD-NPs. (D) Representative fluorescence microscopy image of cardiac tissue sections following DHE staining. (E) Schematic illustration of the preparation of Mn_3O_4@PDA-MSCs and their application for in vivo MRI tracking and microenvironment modulation to

enhance myocardial infarction therapy. (F) Comparison of the fitted R1 relaxation curves of Mn_3O_4 and Mn_3O_4@PDA at pH 7.0. (G) Representative *T1*-weighted and pseudocolor images of Mn_3O_4 and Mn_3O_4@PDA at different concentrations in water. (A-D) Reproduced with permission [114]. Copyright 2024, Wiley-VCH GmbH. (E-G) Reproduced with permission [115]. Copyright 2024, Wiley-VCH GmbH.

3.3 Targeted therapy of atherosclerotic microenvironment

3.3.1 Therapy for Lipid Deposition and Foam Cell Formation

In the heterogeneous plaque microenvironment, lipid deposition and the formation of foam cells are the decisive initial pathological processes [116-118]. The accumulation of oxLDL in the subendothelial layer can directly trigger atherosclerosis [119-122]. Macrophages take up oxLDL through receptor-mediated clearance and further transform into lipid-rich foam cells [123, 124]. The accumulation of foam cells not only indicates plaque formation but also triggers local inflammatory responses by secreting cytokines. Matrix metalloproteinases (MMPs) result in matrix degradation and thinning of the fibrous cap, thereby promoting plaque progression and increasing the risk of rupture [125-127]. Consequently, the therapy of atherosclerosis requires the selective reduction of lipid load and the reversal of foam cells [128-130]. Nanomedicine can achieve precise delivery of lipid regulators, providing an efficient intervention method for regulating this fundamental pathological mechanism [131].

For instance, a recently developed multi-valent nanosystem siTTENPs comprising targeting peptides, nucleic acids (siTRPM2) and β-cyclodextrin to inhibit lipid entry and promote its clearance for the precise therapy of atherosclerotic CVDs (**Fig. 8A**) [132]. Specifically, the surface peptides were modified to target macrophages at the lesion site, aiming to facilitate drug delivery to the source of the plaque cells. Once released, siTRPM2 could reduce macrophage uptake of oxLDL; and β-cyclodextrin structure could promote the active excretion of deposited cholesterol. Thus, this nanosystem effectively restored cholesterol homeostasis, reduced inflammation, and

ultimately significantly reversed atherosclerotic plaques. The siTTENPs platform integrated targeting of the lesion, gene silencing, and cholesterol excretion functions, achieving a significant reduction in plaque burden in the ApoE$^{-/-}$ mouse model. This multifunctional nanodelivery system has potential in simultaneously regulating lipid deposition and inflammatory responses within plaques. Nevertheless, the analysis of organ distribution revealed that these nanoparticles primarily accumulated non-specifically in metabolic organs, namely the liver and kidneys. Since the percentage of injected dose (%ID/g) for quantitative biodistribution was not reported, there was still a need for rigorous determination of their true targeting efficiency relative to reticuloendothelial clearance.

Building on the principle of multifunctional nanotherapeutics, other strategies have sought to regulate additional, complementary aspects of the plaque microenvironment, such as oxidative stress and platelet aggregation. In a notable example, researchers developed a bimetallic platinum-cerium "nano-raspberry" DPTP NRs that provided a synergistic, two-pronged approach (**Fig. 8B, C**) [133]. First, the unique high-surface-area structure of the nano-raspberry itself possessed potent ROS scavenging activity, mimicking antioxidant enzymes like SOD and catalase (CAT) (**Fig. 8D, E**). This intrinsic therapeutic property allowed it to alleviate the high-oxidative-stress environment within the plaque, reducing the formation of oxidized LDL and thereby inhibiting the genesis of foam cells. Second, this nanoplatform was loaded with ticagrelor, a potent P2Y12 inhibitor, designed to attenuate the massive platelet aggregation that contributed to plaque growth and triggered acute thrombotic events. This comprehensive approach attenuated the plaque progression in ApoE$^{-/-}$ mice and regulated their inflammatory microenvironment. However, the DPTP NRs were easily extensively and non-specifically taken up by the reticuloendothelial system due to its reliance on passive extravasation. The organ biodistribution indicated that they mainly accumulated in the liver and spleen. Moreover, the absolute proportion of the injected

dose reaching the vascular lesion sites was not quantitatively reported in %ID/g form, thus making it impossible to clearly determine their true plaque-targeting efficiency.

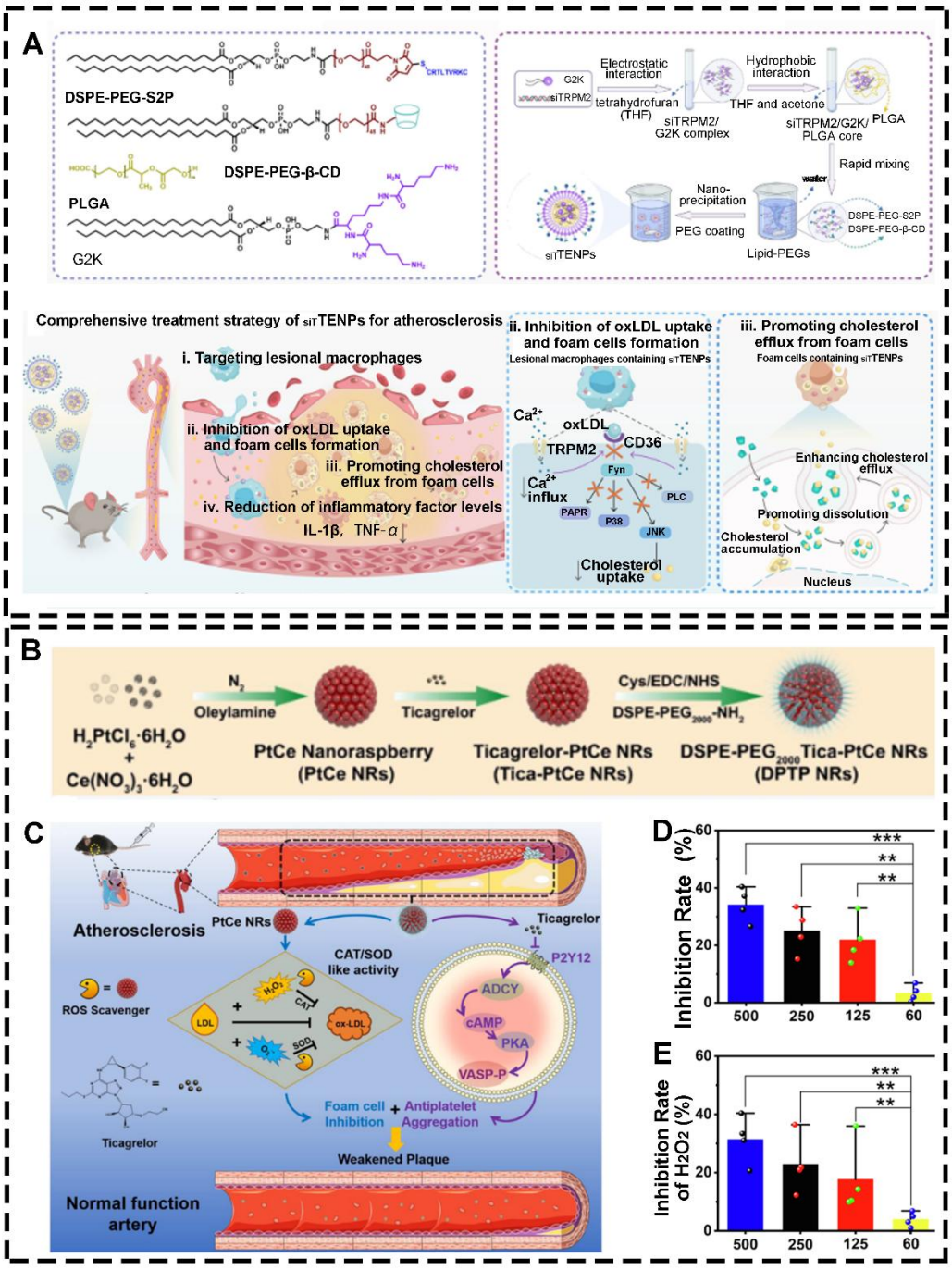


Fig. 8. (A) Schematic illustration of the preparation process of siTTENPs and their therapeutic mechanism against atherosclerosis. (B) Schematic illustration of the preparation of the nanocomposite. (C) Schematic illustration of Pt-Ce bimetallic nano-raspberries for the treatment of atherosclerosis through the synergistic inhibition of foam cell formation and P2Y12-targeted platelet aggregation. (D) Superoxide anion-

scavenging efficiency of DPTP NRs at different concentrations. (E) H_2O_2-scavenging efficiency of DPTP NRs at different concentrations. (A) Reproduced with permission [132]. Copyright 2025, Wiley-VCH GmbH. (B-E) Reproduced with permission [133]. Copyright 2022, Elsevier.

Furthermore, researchers developed palladium hydride nanopocket cubes ($PdH_{0.12}$ NPCs) to combine the inherent functions of nanoparticles with their drug-loading characteristics [134]. This approach redefined the essence of traditional therapeutic drug-loading by storing hydrogen gas (H_2) within the palladium lattice. Moreover, the hard component of PdH0.12 NPCs relied on the inherent antioxidant capacity of palladium nanocubes, which could efficiently eliminate ROS to reduce oxLDL uptake. The soft component came from the therapeutic hydrogen gas released when the lesion was excited by near-infrared light (NIR-II). The released hydrogen gas served as a signaling molecule, promoting the active excretion of cholesterol in foam cells by upregulating the cholesterol transport pathway mediated by PPAR-γ. The catalytic component of this nanoplatform reduced lipid entry, while the gas therapy responsive to stimulation promoted lipid excretion, thereby helping to regulate lipid accumulation and the formation of foam cells. In summary, this presents a treatment strategy oriented towards the microenvironment through simultaneously targeting two aspects of lipid metabolism.

3.3.2 Anti-inflammatory and immune cell infiltration therapy

The atherosclerotic microenvironment is a dynamic and immunologically active microenvironment with continuous inflammatory responses and coordinated recruitment of immune cells [135-137]. Damaged vascular cells and accumulated fat cells attract a large number of immune cells to the vessel wall [138-140]. The aggregation of these cells leads to continuous deterioration of inflammation, decreased stability of the plaque, and an increased likelihood of rupture, which can trigger

myocardial infarction or cerebral stroke [141-143]. Therefore, a cornerstone of therapy is to precisely inhibit the local inflammatory response without disrupting normal immunity [144-147].

For instance, Wei *et al.* developed a dual-mode-driven nanomotor composed of anti-CD36 antibody and rapamycin for achieving the targeted treatment of plaques (**Fig. 9A**) [148]. The anti-CD36 antibody facilitated the targeting of lesional macrophages. Additionally, rapamycin alleviated inflammation and promoted autophagy, thereby promoting plaque regression (**Fig. 9B, C**). This nanoplatform integrated multiple functions and significantly reduced the lipid plaque load in $ApoE^{-/-}$ mice. However, in vivo tracking mainly relied on qualitative *T1-weighted* MRI, which also highlighted the significant amount of non-targeted retention in the hepatobiliary system. Moreover, since the percentage of the actual injected dose that reaches the aortic lesion site (in %ID/g) has not been reported, the comparison between the absolute targeting efficiency and the reticuloendothelial clearance rate has not yet been quantified.

To address the oxidative stress caused by ROS and the pro-inflammatory signaling pathway mediated by TRAF6, Yang *et al.* designed two different targeted nanosystems for macrophages to deliver ROS scavengers, platinum nanoparticles (37pA-PtLNP), and TRAF6 inhibitors (37pA-LNP/6877002) [149]. Although the platinum nanoparticles displayed significant effects, they instead induced the expression of the pro-inflammatory enzyme inducible nitric oxide synthase (iNOS). Interestingly, the TRAF6 inhibitor not only inhibited the main inflammatory pathways but also synergistically counteracted the abnormal upregulation of iNOS caused by the platinum nanoparticles. This study demonstrated that nanomedicine could regulate multiple inflammatory pathways in the pathological microenvironment, especially at the immunological level, establishing a mechanism intervention strategy for the treatment of atherosclerosis.

Furthermore, Chen *et al.* proposed additional CVDs treatment strategies for metabolic regulation apart from immunomodulation [150]. They developed a

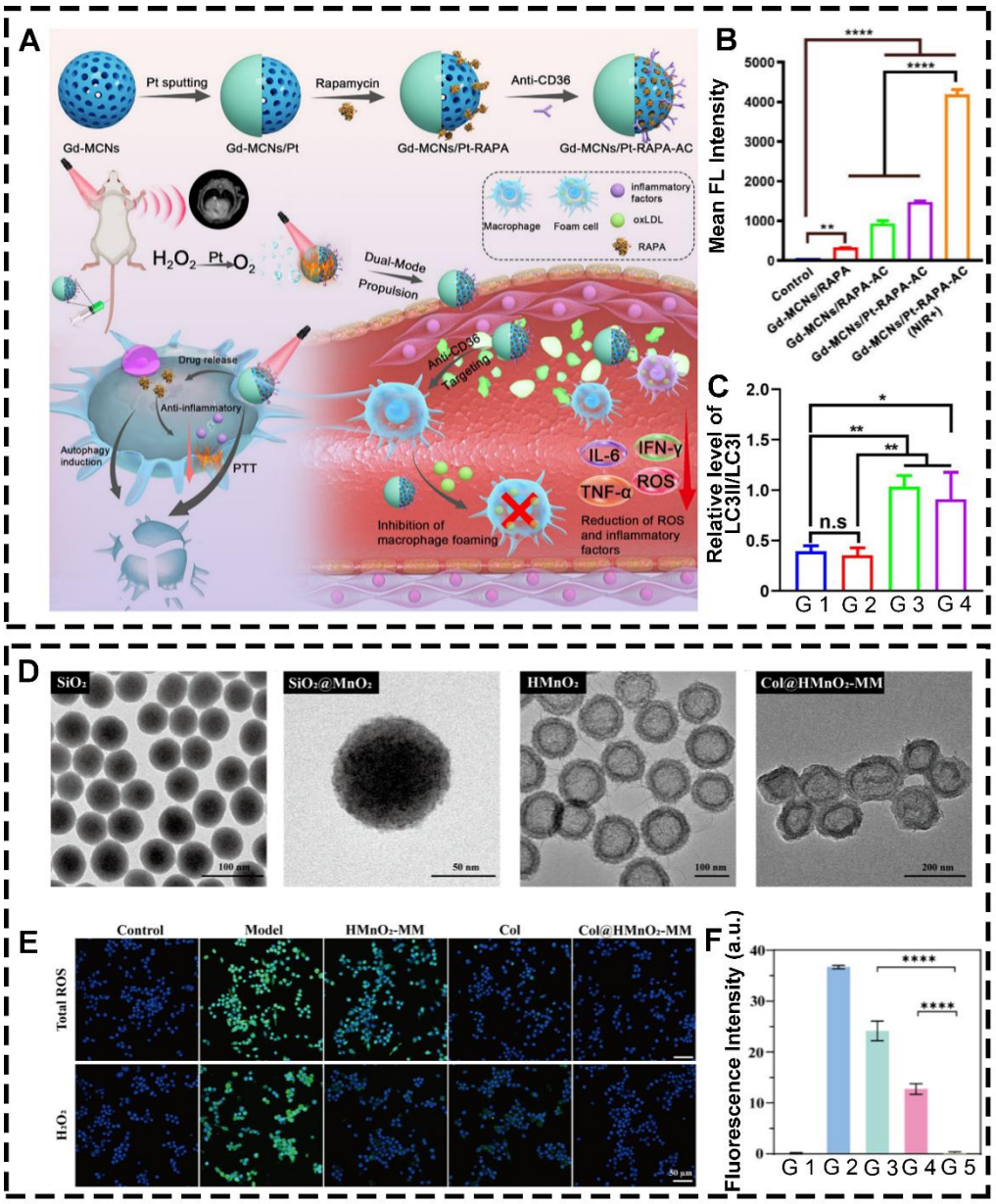


Fig. 9. (A) Schematic illustration of the construction of Gd-MCNs/Pt-RAPA-AC dual-mode nanomotors and their synergistic regulation of photothermal effects, inflammation, and autophagy to enhance the therapeutic efficacy of hyperthermia for atherosclerosis. (B) Cellular uptake by RAW264.7 cells under different conditions, quantified by relative fluorescence intensity. (C) Relative expression level of the autophagy marker LC3 determined by Western blotting. (D) Representative transmission electron microscopy (TEM) images of SiO_2, SiO_2@MnO_2, $HMnO_2$, and Col@$HMnO_2$-MM. (E) Representative confocal laser scanning microscopy (CLSM) images showing total ROS levels in RAW264.7 cells following different treatments.

(F) Quantitative analysis of the fluorescence intensity shown in (E). (A-C) Reproduced with permission [148]. Copyright 2025, BMC (BioMed Central). (D-F) Reproduced with permission [150]. Copyright 2024, BMC (BioMed Central).

macrophage membrane-functionalized hollow manganese dioxide nanomedicine (Col@HMnO$_2$-MM) (**Fig. 9D**). This platform offered a multifaceted approach to microenvironment regulation: the macrophage membrane provided homologous targeting to inflammatory sites while the manganese dioxide core served as a nanozyme, catalytically neutralizing ROS and, crucially, alleviating plaque hypoxia by decomposing endogenous H_2O_2 into oxygen (**Fig. 9E, F**). This oxygenation directly countered the hypoxia-induced inhibition of cholesterol efflux transporters (ABCA1/ABCG1), thus restoring a crucial metabolic function for foam cell clearance. Simultaneously, the loaded anti-inflammatory drug, colchicine, worked in concert with the ROS scavenging to suppress the inflammatory storm. This study demonstrates how a single nanomedicine can simultaneously regulate the immune, chemical and metabolic aspects of the atherosclerotic microenvironment, highlighting the comprehensive approach to treating atherosclerosis.

3.3.3 Extracellular Matrix Remodeling and Plaque Stability

Within the complex microenvironment of atherosclerotic plaques, structural integrity is frequently undermined by ECM degradation, a key determinant of plaque instability [151-153]. The surface of the vascular plaque originally has a thick layer of collagen protein as a protective layer, which can prevent the plaque from rupturing [154-156]. However, long-term vascular inflammation will activate some destructive enzymes, which continuously break down and consume this layer of collagen, causing the protective layer to become thinner and more fragile [157-162]. Once it cannot withstand the pressure of blood flow and ruptures, a thrombus will form rapidly, triggering myocardial infarction or cerebral stroke [163-166]. Therefore, protecting

collagen and strengthening this protective layer have become the core strategy for preventing sudden fatal cardiovascular events.

For instance, Hou *et al.* developed a low-intensity focused ultrasound (LIFU)-responsive nanomedicine designed to directly eliminate the source of ECM-degrading enzymes: the plaque macrophages (**Fig. 10A**) [167]. The nanosystem was composed of nanoparticles loaded with the phase-change agent perfluorohexane (PFH), and was specifically targeted to scavenger receptors on macrophages through the functionalization of the surface with dextran sulfate (**Fig. 10B, C**). When LIFU irradiation was performed at the plaque site, PFH underwent acoustic droplet vaporization (ADV) - a rapid liquid-to-gas transformation process (**Fig. 10D, E**). This ADV effect generated local mechanical forces, inducing apoptosis of macrophages. This method effectively blocked the main source of MMPs by depleting these crucial inflammatory cells, thereby maintaining the integrity of the fibrous cap and significantly enhancing the stability of the plaque (**Fig. 10F, G**). This study utilized physical energy to regulate the cellular components in the pathological microenvironment, alleviating matrix metalloproteinase degradation and regulating the characteristics related to plaque vulnerability. Nevertheless, *ex vivo* organ imaging revealed that these nanoparticles were mainly cleared by the reticuloendothelial system and accumulated non-specifically in the liver and spleen. Moreover, the absolute delivery efficiency at the vascular lesion sites has not yet been quantified since no quantitative biodistribution data (percentage of injected dose, %ID/g) were reported.

Although eliminating macrophages is a strategy to protect the fibrous cap, the stability of the plaque is also severely disrupted due to VSMCs, which may further trigger ECM degradation. To prevent this process, Fellows *et al.* studied a destructive feedback loop and explored the role of the transcription factor FOXO3a in this process [168]. The activation of FOXO3a in VSMCs not only directly induced cell death but also significantly upregulated the expression and release of MMP-13, thereby accelerating the death of adjacent VSMCs. In summary, the loss of ECM-producing

cells actually accelerated ECM degradation, providing important insights into the intrinsic pathways that drive plaque instability.

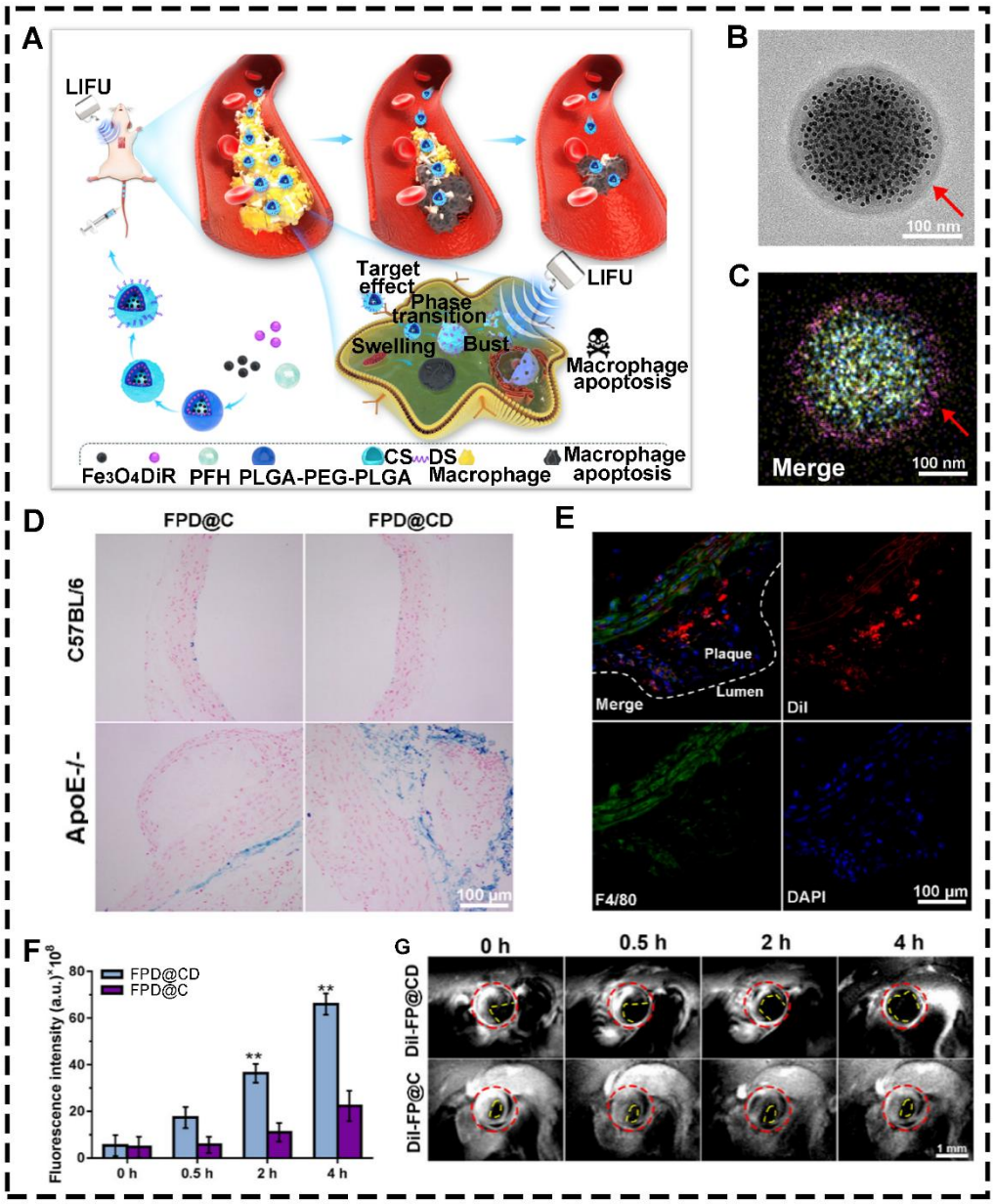


Fig. 10. (A) Schematic illustration of the preparation of FPD@Cd nanoparticles and their effects on RAW 264.7 cells and vulnerable atherosclerotic plaques. (B) Representative transmission electron microscopy (TEM) image of DII-FP@CD nanoparticles. (C) Representative elemental mapping image of DII-FP@CD nanoparticles. (D) Representative *ex vivo* aortic sections from mice subjected to different drug treatments and stained with Prussian blue. (E) Representative immunofluorescence images showing merged signals of DiI-FP@CD NPs (red), F4/80-

positive macrophages (green), and DAPI-stained nuclei (blue). (F) Quantitative analysis of fluorescence intensity in the aortic arch of $ApoE^{-/-}$ mice at different time points following injection in targeted and non-targeted groups. (G) Cross-sectional *T2*-weighted images of ascending aortic plaques at different time points in targeted and non-targeted $ApoE^{-/-}$ mice. (A-G) Reproduced with permission [167]. Copyright 2022, KeAi Communications Co., Ltd.

3.3.4 Thrombosis Risk Interventions

Atherosclerotic plaque rupture constitutes a pivotal pathological event in cardiovascular disease, inducing abrupt and profound remodeling of the intra-plaque microenvironment and precipitating a sharp rise in thrombotic risk [169-171]. Rupture, or severe erosion, of the thin, collagen-depleted fibrous cap in a vulnerable plaque exposes the highly thrombogenic lipid-rich necrotic core and underlying ECM proteins (*e.g.*, collagen I, von Willebrand factor, and fibronectin) to circulating blood [172-173]. Once the plaque ruptures, the internal necrotic substances will immediately trigger a strong coagulation response [174-176]. Platelets rapidly aggregate and a large number of clotting substances accumulate. Within a very short period of time, a thrombus will form and block the blood vessel, resulting in an acute myocardial infarction or stroke [177]. Therefore, blocking the thrombus rupture triggered by plaque rupture at its source is an important strategy in the treatment of vascular hardening.

Nanomedicine can directly deliver antithrombotic drugs to the sites of plaque rupture or high-risk plaques, thereby achieving local prevention of thrombosis [178-180]. For instance, Cheng *et al.* fabricated platelet membrane-camouflaged biomimetic nanoparticles HMTL@PM to simultaneously deliver the hirudin and lumbrokinase for mitigating atherosclerosis and thrombosis [181]. These nanoparticles leveraged the platelet membrane shell to evade immune clearance and selectively target thrombus lesions through assembling tannic acid and Mn^{2+}. Within the weakly acidic microenvironment of atherosclerotic plaques, HMTL@PM underwent responsive

dissociation to release hirudin and lumbrokinase. This triggered delivery not only exerted synergic anticoagulation and thrombolysis to prevent vessel occlusion, but also attenuated local inflammation and promoted cholesterol efflux to stabilize atheromatous plaques. This study utilized platelet membrane-coated nanoparticles to deliver anticoagulant drugs to areas prone to thrombosis, demonstrating the ability of nanomedicine to achieve local regulation of thrombus responses in high-risk atherosclerotic plaques.

Apart from bionic nanomedicine, the stimulus-responsive therapeutic strategy is also an advanced approach that enables precise treatment of the affected area. Liu *et al.* developed a dual-efficiency nanoplatform utilizing up-conversion nanoparticles (UCNPs) for targeted thrombolytic and anticoagulant therapy (**Fig. 11A-C**) [182]. Significantly, this nanoplatform could directly convert deep-penetrating near-infrared (NIR) light at the thrombus site into ultraviolet/blue light. The tirofiban modified on the surface of the nanoparticles could target the receptors on activated platelets and guide the nanoplatform to the thrombus site. Near-infrared light irradiation triggered the controlled release of urokinase (UK) to dissolve the thrombus and release NO, preventing further coagulation by inhibiting platelet aggregation (**Fig. 11D-F**). This innovative nanoplatform achieves synergistic thrombolytic and anticoagulant effects, and constructs an efficient imaging, diagnosis, and treatment system.

In contrast, Xu *et al.* designed a self-regulating delivery system that could internally respond to pathological coagulation cascade reactions without external stimulation (**Fig. 11G, H**) [183]. They developed a nanogel encapsulating recombinant hirudin (a thrombolytic peptide) and targeting thrombus segments for treating thrombosis. Specifically, this nanogel was constructed using cross-linking agents that could be cleaved by thrombin, and its surface was modified with thrombus-targeting peptides to ensure its aggregation at the thrombus formation site. Additionally, recombinant hirudin was a potent thrombin inhibitor and is commonly utilized to treat thrombosis. When there was excessive thrombin in thrombosis formation, the across-linking agents

would be cleaved, inducing the nanogel to dissociate and release hirudin (**Fig. 11I-K**). Interestingly, the released hirudin subsequently inhibited thrombin, slowing down the cleavage process of the cross-linking agents and the release of the drug, forming a self-regulating negative feedback loop. This intelligent design enables the nanogel to release anticoagulants according to the severity of the thrombus environment, thereby enhancing anticoagulant activity when needed and minimizing the risk of systemic bleeding.

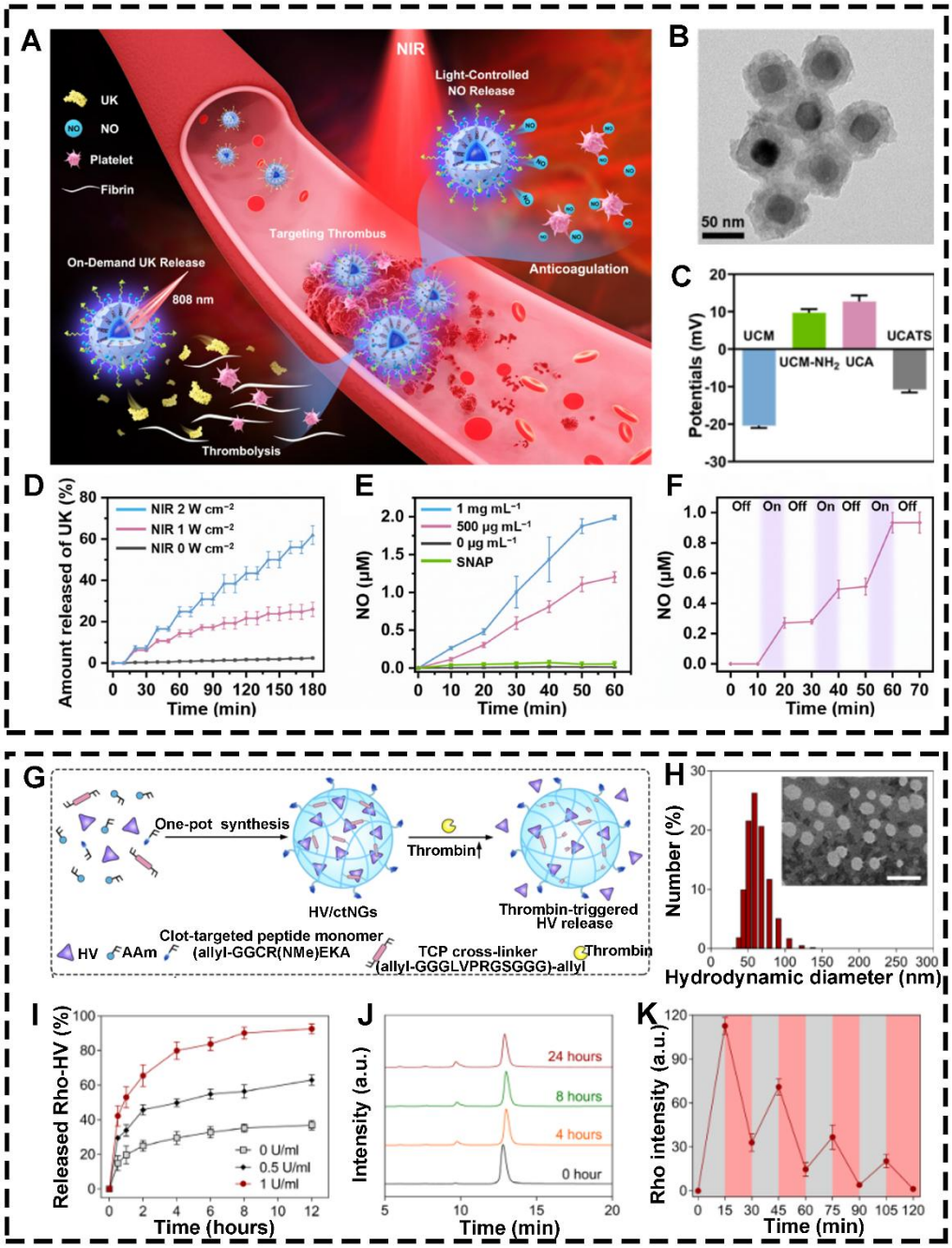


Fig. 11. (A) Schematic illustration of the NIR-triggered co-delivery of urokinase (UK) and NO from UCATS-UK for targeted thrombolytic and anticoagulant therapy. (B) Representative transmission electron microscopy (TEM) image of UCATS nanoparticles. (C) Comparison of the zeta potentials of different nanoparticles. (D) Controlled release of UK from UCATS-UK triggered by NIR irradiation. (E) NO release from UCATS induced by NIR irradiation or SNAP at different concentrations. (F) Switchable NO release behavior under 808 nm NIR irradiation. (G) Schematic illustration of the synthesis of HV/ctNGs and the thrombin-responsive release of HV. (H) Representative histogram of the hydrodynamic diameter distribution and a representative TEM image of HV/ctNGs. (I) Thrombin-responsive release of Rho-HV from Rho-HV/ctNGs at different enzyme concentrations. (J) Representative HPLC chromatograms showing the time-dependent cleavage of TCP crosslinkers by thrombin in the presence of HV. (K) Rho-HV release from Rho-HV/ctNGs following multiple cycles of thrombin incubation. (A-F) Reproduced with permission [182]. Copyright 2022, KeAi Communications Co., Ltd. (G-K) Reproduced with permission [183]. Copyright 2020, American Association for the Advancement of Science.

4. Cross-Cutting Design Strategies and Mechanisms for Cardiovascular Microenvironment Modulation

Based on the applications for diseases discussed in Section 3, this section integrates the cross-disciplinary design principles underlying the regulation of the cardiovascular microenvironment. We do not repeat the case studies specific to individual diseases, but instead conduct a critical comparison based on the targeting strategies and therapeutic mechanisms of the nanomedicine platform [184-186]. CVDs are essentially complex and dynamically changing pathological conditions, including chronic inflammation, oxidative stress, dysregulation of extracellular matrix remodeling, impaired angiogenesis, and metabolic dysfunction [187-188]. Nanomedicine provides an effective platform for cell or tissue-specific delivery, responsive release, and

synergistic treatment [189]. This section systematically explores how nanomedicine can be ingeniously designed to play a role in precisely treating CVDs by regulating the microenvironment of the cardiovascular system.

4.1 Nanomedicine for regulating the inflammatory microenvironment

4.1.1 Nanocarriers Targeting Inflammatory Cells

The persistence of inflammation depends on the recruitment and accumulation of immune cells in the pathological microenvironment, which is the core pathogenic mechanism of most CVDs [190-192]. Therefore, regulating these immune-inflammatory cells is a promising therapeutic strategy. This section focuses on how to precisely deliver therapeutic drugs to the inflammatory cells in the cardiovascular tissues through carefully designed nanocarriers. This targeting not only enhances the local accumulation of the drugs at the pathological site but also improves biological safety, promoting the recovery of immune inflammation in the microenvironment [193-195].

For instance, Liu *et al.* developed a biomimetic nanoplatform modified by the surface of macrophage membranes for the precise diagnosis and treatment of atherosclerosis (**Fig. 12A-C**) [196]. Significantly, the precise arrangement during the assembly of the nanoplatform could preserve the functions of surface proteins, enabling it to target the inflammatory areas within blood vessels. To achieve this goal, researchers introduced specific peptide segments that bound to phosphatidylserine onto the biomimetic nanoplatform. Phosphatidylserine was mainly located in the inner layer of the macrophage membrane and enabled the membrane coating layer to be correctly oriented. In summary, this nanoplatform employed a dual activation system that required two different environmental trigger factors, which were precisely the characteristics of atherosclerotic plaques (**Fig. 12D, E**). The first key, high levels of ROS, was needed to release the therapeutic payload (rapamycin) and a fluorescent probe; the second key, a lipid-rich environment within foam cells, was then necessary

to switch on the probe's fluorescence. This "AND" logic gate strategy significantly enhanced the specificity of both imaging and drug delivery. This biomimetic nanoscale platform demonstrated excellent aggregation ability at the lesion site, significantly reducing the size of the plaque and the degree of inflammation in the mouse model of atherosclerosis. This showcased an advanced strategy in nanomedicine for regulating the pathological microenvironment. This study constructed a system that could respond to molecular signals related to atherosclerotic pathology, achieving targeted therapeutic delivery while regulating the local disease microenvironment.

Based on the mechanism of microenvironment-responsive nanomedicine, Fang *et al.* developed a novel intelligent nanocarrier comprising polymer PLGA-PEG-c(RGDfC) peptide and rapamycin for precise treatment of atherosclerosis [197]. Different from the biomimetic design, this system achieved active targeting by introducing the polymer PLGA-PEG-c(RGDfC) peptide. This peptide could specifically bind to the integrin αvβ3 receptors accumulated in inflammatory endothelial cells at the lesion. To achieve the response mechanism of drug release, the nanoparticles were decorated to be sensitive to a lysosomal cysteine protease cathepsin K (CTSK), which was significantly enriched in atherosclerotic plaques. Under the stimulation of CTSK, rapamycin was released, which could effectively accumulate at the atherosclerotic lesion site. In mouse experiments, this nanocomposite successfully inhibited local and systemic inflammation, significantly regressing the progression of atherosclerosis.

Further advancing the application of biomimicry for targeting inflammatory cells, Liu *et al.* shifted the focus from macrophages to neutrophils and from small-molecule drugs to gene therapy [198]. They developed a nanoplatform by coating a metal-organic framework (ZIF-8) loaded with an antisense oligonucleotide against microRNA-155 (anti-miR-155) with a neutrophil cell membrane (**Fig. 12F, G**). This design cleverly exploited the natural inflammatory homing mechanism of neutrophils. The neutrophil membrane protein CD18 on the nanoparticle's surface actively targeted its

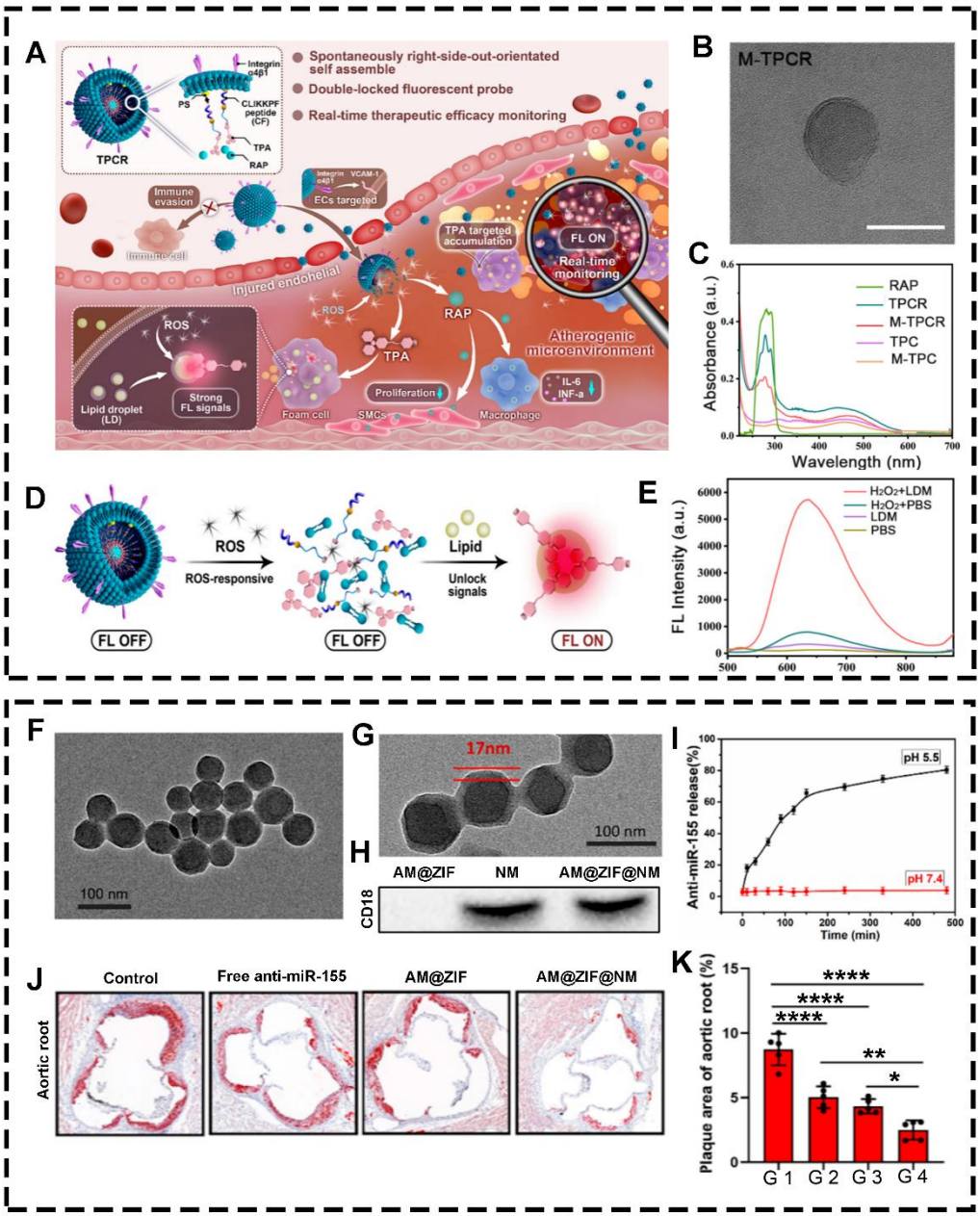


Fig. 12. (A) Schematic illustration of the fabrication of ROS-responsive nanoparticles driven by spontaneous inside-to-outside coupling of the inner leaflet of the cell membrane and their application in real-time therapeutic monitoring of atherosclerosis. (B) Representative transmission electron microscopy (TEM) image of M-TPCR. (C) Absorption spectra of M-TPC in water and RAP. (D) Schematic illustration of the ROS-responsive lipid-unlocking fluorescent probe (M-TPCR). (E) Comparison of the fluorescence spectra of M-TPCR after incubation with H_2O_2 in PBS and LDM. (F) Representative TEM image of AM@ZIF nanoparticles. (G) Representative TEM image

of AM@ZIF@NM nanoparticles. (H) Comparative Western blot analysis of CD18 expression in AM@ZIF, NM, and AM@ZIF@NM nanoparticles. (I) Release profiles of anti-miR-155 from AM@ZIF@NM nanoparticles at pH 7.4 and 5.5 over time. (J) Representative images of frozen aortic root sections stained with Oil Red O. (K) Quantitative analysis corresponding to (J). G1, Control; G2, free anti-miR-155; G3, AM@ZIF; G4, AM@ZIF@NM. (A-E) Reproduced with permission [196]. Copyright 2025, Elsevier. (F-K) Reproduced with permission [198]. Copyright 2023, American Chemical Society.

corresponding receptor, ICAM-1, which was overexpressed on the inflamed endothelial cells of atherosclerotic plaques (**Fig. 12H**). Once internalized, the pH-sensitive ZIF-8 core efficiently released the anti-miR-155 payload into the cytoplasm (**Fig. 12I**). This suppresses miR-155, a critical regulator of inflammation, thereby attenuating NF-κB signaling and reducing the expression of pro-inflammatory genes. In animal models, this neutrophil-mimicking nanotherapy significantly inhibited inflammation and alleviated atherosclerosis (**Fig. 12J, K**).

Collectively, these studies demonstrate the therapeutic potential of nanomedicine to dynamically regulate the pathological cardiovascular microenvironment. By engineering nanocarriers that selectively sense and respond to disease-associated biochemical cues, including cell-surface receptors (*e.g.*, integrins), dysregulated enzymatic activity (*e.g.*, cathepsin K), or endogenous adhesion pathways, researchers achieve spatiotemporally controlled delivery of diverse therapeutics, ranging from small-molecule inhibitors to nucleic acid–based gene-silencing agents. This targeted intervention enables precise modulation of local pathophysiological processes and constitutes a mechanistically grounded advancement in cardiovascular therapeutics.

4.1.2 Delivery of Anti-Inflammatory Drugs

While targeted delivery to inflammatory cells represents a refined therapeutic strategy, broad and efficient delivery of anti-inflammatory agents remains equally critical for modulating the pathological inflammatory microenvironment [199-201]. Nanoformulations for anti-inflammatory drug delivery mainly include liposomes, polymeric preparations, biomacromolecules, inorganic nanoformulations and biomimetic nanoformulations [202-204]. These nanoformulations are specifically engineered to achieve targeted accumulation and stimuli-responsive release in inflamed tissues [205-207]. Nanoformulations can enhance the bioavailability and safety of drugs, enable controllable sustained release or responsive release, and significantly improve the therapeutic efficacy of CVDs [208-211]. Moreover, nanoformulations are capable of inhibiting the chronic inflammation that drives the progression of cardiovascular diseases, thereby facilitating the restoration of tissue homeostasis [212, 213]. For instance, a study developed nanoscale coordination polymers (Fe-Cur CPs) loaded with curcumin to simultaneously act on the inflammation and oxidative stress for achieving synergistic treatment of atherosclerosis [214]. Significantly, these nanoparticles combined the anti-inflammatory properties of curcumin with the ability of iron-based polymers to eliminate ROS. The results of *in vitro* experiments demonstrated that Fe-Cur CPs inhibited monocyte adhesion and the production of inflammatory factors, and significantly prevented the formation of foam cells. Mice exhibited reduced plaque burden, alleviated inflammation and oxidative stress in the lesion after injection of Fe-Cur CPs. In summary, this study demonstrated that Fe-Cur CPs enhanced plaque stability and presented a multi-targeted nanomedicine strategy that regulates the pathological microenvironment.

Similarly, another advanced strategy employed a thermosensitive diagnostic nucleic acid gel specifically designed for targeting inflammatory endothelial cells, consisting of NF-κB siRNA, VCAM-1 targeting peptide, and gadolinium-DOTA contrast agent for the treatment and diagnosis of CVDs (**Fig. 13A**) [215]. NF-κB siRNA was a small inhibitory nucleic acid that could specifically target and inhibit the

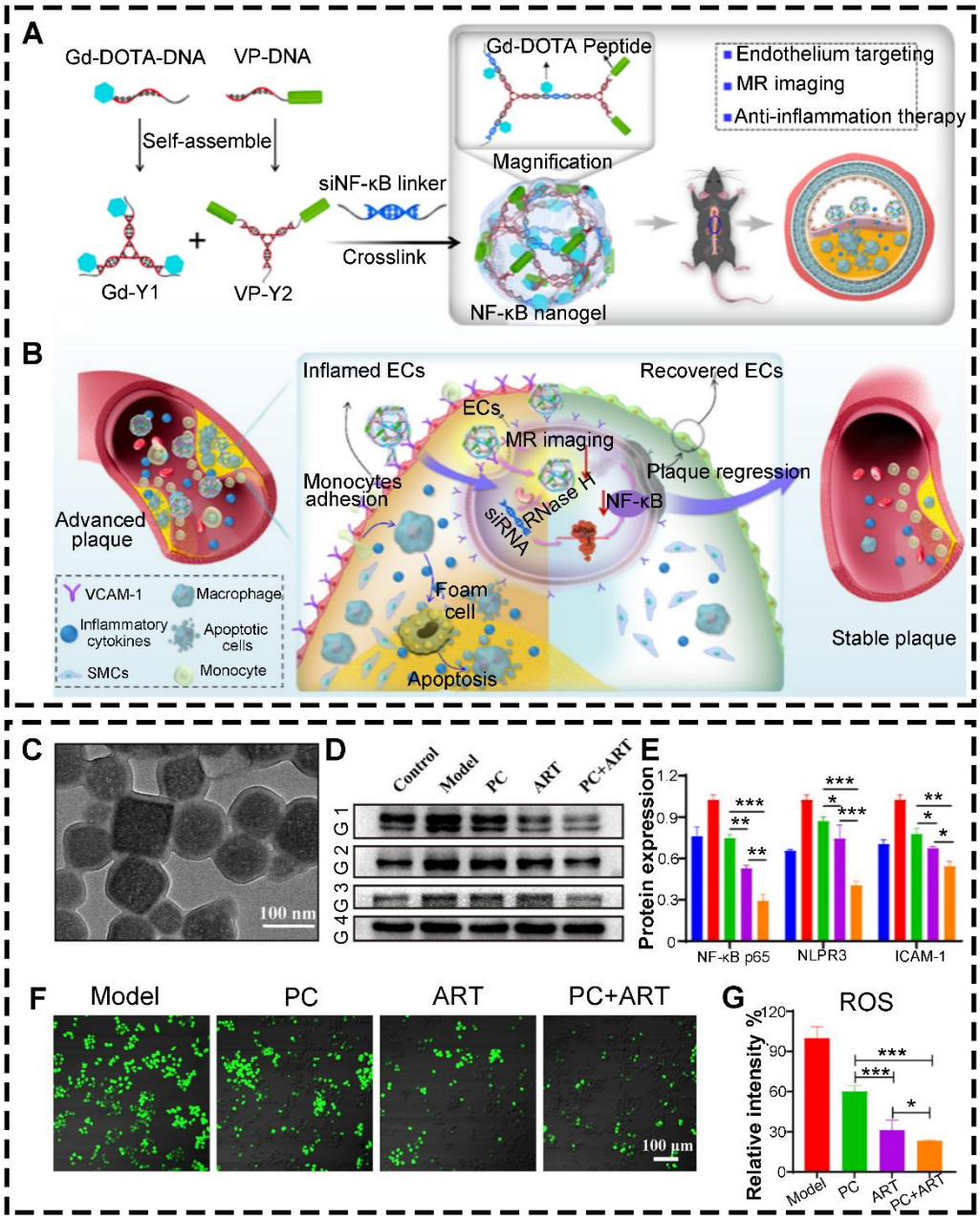


Fig. 13. (A) Schematic illustration of the self-assembly of Y-shaped Gd-Y1 and Vp-Y2 into NF-κB-responsive nanogels. (B) Schematic illustration of the intracellular anti-inflammatory mechanism and in vivo performance of NF-κB-responsive nanogels. (C) Representative transmission electron microscopy (TEM) image of HA-M@PB@(PC+ART) NPs. (D) Western blot analysis of NF-κB, NLRP3, and ICAM-1 expression in different treatment groups. (E) Quantitative analysis of the Western blot results shown in (D). (F) Confocal microscopy images showing intracellular ROS levels in activated RAW264.7 cells treated with PC and ART. (G) Quantitative analysis of the

fluorescence intensity shown in (F). (A-B) Reproduced with permission [215]. Copyright 2025, Elsevier. (C-G) Reproduced with permission [216]. Copyright 2022, Elsevier.

inflammatory factor NF-κB. The VCAM-1 targeting peptide enabled the nanogel to target the lesion area, as VCAM-1 was highly expressed in inflammatory endothelial cells. Additionally, the gadolinium-DOTA contrast agent served as an imaging agent for MRI, playing a diagnostic role. This nanogel effectively reversed the inflammatory state, reduced the expression of cytokines and adhesion molecules, and significantly reduced the atherosclerotic plaques in the blood vessels of the mouse model (**Fig. 13B**). Particularly importantly, the introduction of the MRI contrast agent enabled the visualization of the plaques, thereby facilitating precise diagnosis and timely assessment of treatment effects. This combined approach of diagnosis and active regulation of the pathological microenvironment provided a promising treatment strategy for CVDs.

Another promising strategy is to regulate the metabolic disorders of macrophages besides targeting inflammation, which is a pivotal characteristic of the atherosclerotic microenvironment. For instance, Zhou *et al.* developed multifunctional Prussian blue nanoparticles to deliver Artemisinin (ART) and Procyanidins (PC) for the therapy of atherosclerotic plaques [216]. These nanoparticles were coated with a hybrid membrane derived from both macrophages and red blood cells, and further modified with hyaluronic acid (**Fig. 13C**). This sophisticated biomimetic design endowed the system with prolonged circulation, immune evasion, and a high affinity for inflammatory macrophages within the plaque. Once targeted, the nanocomplex orchestrated a dual attack on foam cell formation: ART suppressed lipid influx by inhibiting the NF-κB/NLRP3 inflammatory pathway, while PC promoted cholesterol efflux by activating the AMPK/mTOR/autophagy pathway (**Fig. 13D, E**). Prussian blue nanoparticles could also eliminate ROS, alleviating oxidative stress in the disease microenvironment (**Fig.**

13F, G). This study improved the abnormal lipid metabolism of plaque macrophages, thereby significantly promoting the stability and regression of plaques.

4.1.3 Removal of Inflammatory Mediators

Beyond targeted delivery of anti-inflammatory drugs or cells, an innovative and direct strategy for modulating the inflammatory microenvironment in CVDs entails the selective removal or functional neutralization of pathogenic inflammatory mediators [217-219]. Nanomaterials for inflammatory mediator clearance encompasses a growing class of engineered nanosystems, including cytokine-binding nanoparticles, ROS-scavenging nanocatalysts, and decoy receptor-functionalized vesicles, designed to selectively capture, sequester, or catalytically inactivate pro-inflammatory cytokines, chemokines, ROS, DAMPs, and other key drivers of sterile inflammation in cardiovascular tissues [220-222]. Nanomaterials may prevent the vicious cycle of inflammation by directly eliminating inflammatory factors outside the cells, promoting tissue repair, and overcoming the limitation that traditional drugs can only be effective once they enter the cells [223-227].

A novel class of multifunctional supra-carbon dots, known as MM@Ce-CDs NPs, has been engineered for the targeted diagnosis and treatment of atherosclerosis by modulating the plaque's pathological microenvironment (**Fig. 14A**) [228]. These nanoparticles were created by assembling cerium ions with carbon dots, which were then coated with a macrophage membrane. Within the atherosclerotic plaque, the high concentration of ROS triggered the nanoparticles' cascade enzyme-like activities. This activation facilitated to regulate the inflammatory microenvironment by lowering ROS levels, reducing inflammation, decreasing the infiltration of M1 macrophages, and preventing the formation of foam cells, all of which worked together to inhibit plaque development (**Fig. 14B-D**). The coating of macrophage membranes also enabled nanoparticles to specifically target atherosclerotic lesions, and possessed precise imaging and diagnostic capabilities due to their activated fluorescence and optical

properties. This research had achieved precise treatment of CVDs by intelligently regulating the pathological microenvironment in cardiovascular disease treatment through engineering methods. Specifically, these nanoparticles could respond to inflammation and oxidative stress, and achieved targeted delivery as well as diagnostic imaging functions.

Inspired by the catalytic properties of cerium dioxide, researchers developed hyaluronic acid-guided cerium dioxide nanozyme assemblies (HA-CeO_2 nanoparticles) as a potent ROS scavenger for the treatment of atherosclerosis [229]. Hyaluronic acid (HA) provided stability and biocompatibility to the core of cerium dioxide nanozymes and could specifically target atherosclerotic plaques due to excessive inflammatory macrophages expressing CD44. Interestingly, the introduction of HA not only stabilized the nanozymes but also significantly enhanced their SOD-like activity compared to the control group. These targeted nanozymes could effectively remove excessive ROS, protected macrophages from oxidative damage induced by ROS, and inhibited macrophages from internalizing ox-LDL (**Fig. 14E-G**). This research demonstrates that nanomedicines can directly target inflammatory mediators, thereby restoring the homeostasis of the atherosclerotic pathological microenvironment.

Nanozymes are also a type of molecule used for combined treatment of atherosclerosis due to their ability to eliminate ROS. For instance, a novel method has been developed to prepare a biomimetic nanoscale platform (PCZ@PB NCs) consisting of cerium oxide nanomachines and the antioxidant probucol, which are employed to eliminate ROS for treating atherosclerosis [230]. To achieve targeted delivery, these drug-loaded nanozymes were further coated with platelet membranes. This platelet membrane coating enabled the nanozymes to specifically accumulate at inflammatory atherosclerotic lesions. The cerium oxide nanozymes core could eliminate ROS, while the loaded probucol provided additional antioxidant effects. Together, they synergistically regulated inflammation and inhibited the formation of foam cells. This small molecule-assisted assembly has constructed a sophisticated combined treatment

system that can both reduce inflammatory mediators and deliver drugs, comprehensively regulating the pathological microenvironment in atherosclerosis.

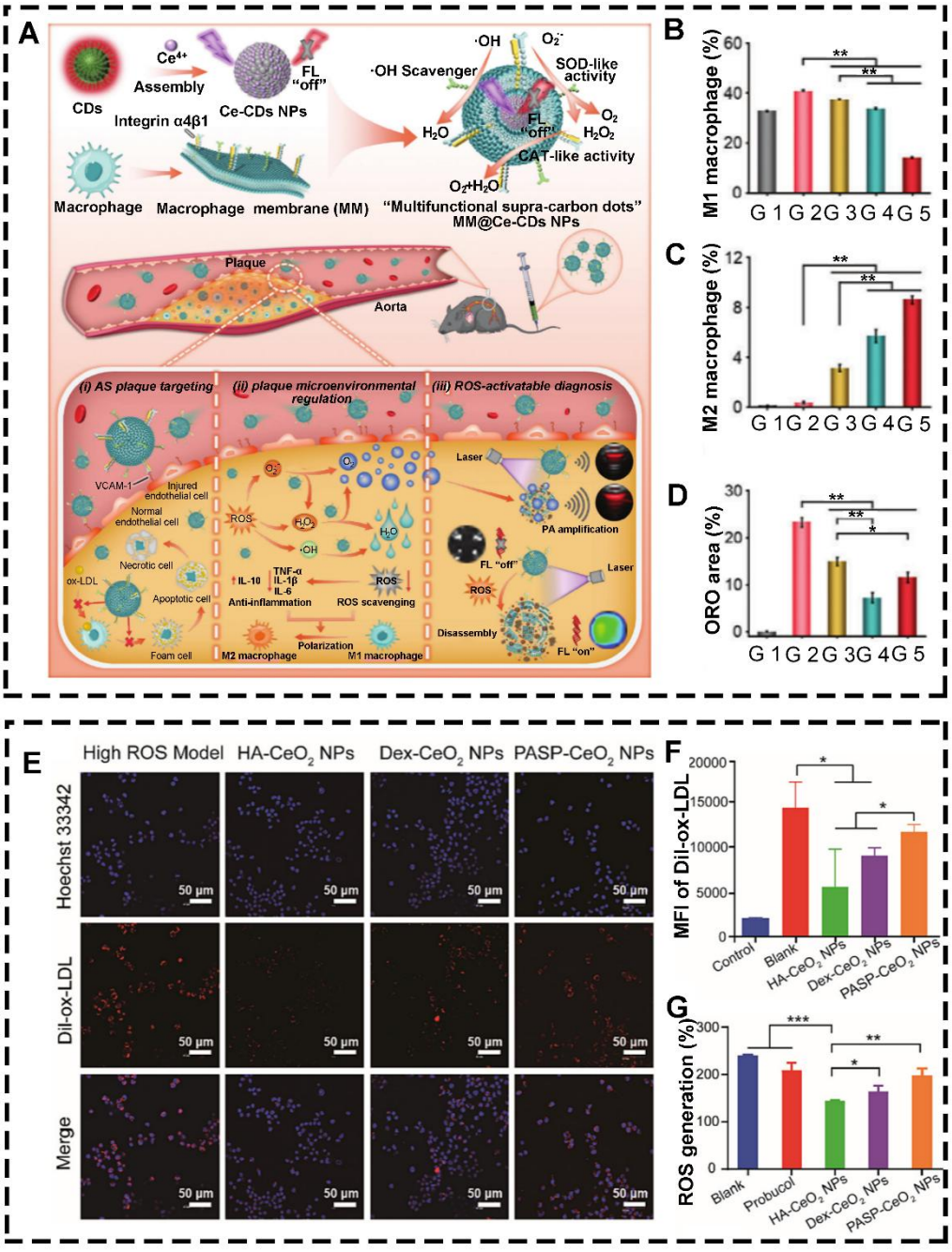


Fig. 14. (A) Schematic diagram of the fabrication and therapeutic mechanism of MM@Ce-CDs. (B) Quantification of M1 macrophage levels in RAW264.7 cells following different treatments, as determined by PE-conjugated CD86 staining. (C) Quantification of M2 macrophage levels in RAW264.7 cells following different treatments, as determined by APC-conjugated CD206 staining. (D) Quantification of Oil Red O staining in RAW264.7 macrophages following different treatments. (E)

Confocal fluorescence imaging of DiI-ox-LDL uptake in cells treated with different nanoparticles. (F) Cellular uptake of DiI-ox-LDL following treatment with nano-CeO_2. (G) Intracellular reactive oxygen species generation in RAW264.7 cells following treatment with nano-CeO_2 and probucol. (A-D) Reproduced with permission [228]. Copyright 2025, Wiley-VCH. (E-G) Reproduced with permission [229]. Copyright 2022, Elsevier.

4.1.4 Inhibition of Leukocyte Chemotaxis and Adhesion

A pivotal early event in the inflammatory cascade within the pathological cardiovascular microenvironment is the spatiotemporally regulated trafficking of leukocytes to sites of injury or disease [231-233]. Therefore, the anti-inflammatory therapy of CVDs can be achieved by specifically inhibiting the chemotaxis and adhesion of white blood cells. This section focuses on the rational design of nanomedicines, aiming to precisely regulate the recruitment and adhesion mechanisms of immune cells on endothelial cells. The carriers prevent the infiltration of immune cells by blocking adhesion or chemotactic signals, thereby inhibiting inflammation in the early stage and reducing cardiovascular damage [234-236]. The precise regulation of white blood cell migration can effectively inhibit pathological inflammation, promoting the restoration of local environmental homeostasis [237].

Liu *et al.* developed an engineered nanoplatform SA-BTST/COL consisting of bovine serum albumin, colchicine and selinexor to intercept and neutralize neutrophils for inhibiting plaque progression (**Fig. 15A**) [238]. Notably, the surface of SA-BTST/COL was modified with sialic acid for dual targeting. When activated neutrophils selectively took it up, this ROS-sensitive nanoscale structure would disintegrate and release the drug (**Fig. 15B, C**). The results demonstrated that SA-BTST/COL significantly reduced cell infiltration and lipid deposition in mice, thereby improving plaque stability (**Fig. 15D, E**). The released colchicine induced cell apoptosis and prevented migration, while the released selinexor inhibited the

inflammatory response of NET formation. Therefore, the SA-BTST/COL nanoplatform effectively sequestered inflammatory triggers, thereby enhancing plaque stability.

Based on the interception of white blood cells, another complementary strategy targeted the interaction between platelets and monocytes that drove lesion formation. Huang *et al.* found that the CXCL8-CXCR2 pathway was a pivotal driver of monocyte recruitment in treating atherosclerotic cardiovascular disease [239]. To block this pathway, they developed a long-circulating biomimetic nanoplatform coated with red blood cell-platelet hybrid membranes (**Fig. 15F**). This nanoparticle had a surface modified with specific antibodies, which could precisely block the CXCR2 receptor on monocytes. By serving as a molecular shield, this "anti-CXCR2 [RBC-P]NP" effectively 'blinds' circulating monocytes to the chemoattractant CXCL8 released by platelets at sites of vascular injury (**Fig. 15G**). This blockade not only physically prevented cell infiltration but also regulated the pro-inflammatory M1 phenotype differentiation by inhibiting the p38α signaling pathway. This nanoscale intervention significantly reduced cell aggregation and plaque accumulation, thereby inhibiting atherosclerosis without increasing the risk of bleeding (**Fig. 15H-J**). This study demonstrates an advanced strategy for cutting off intercellular communication to regulate the microenvironment, which can effectively prevent the recruitment and activation of pathogenic white blood cells.

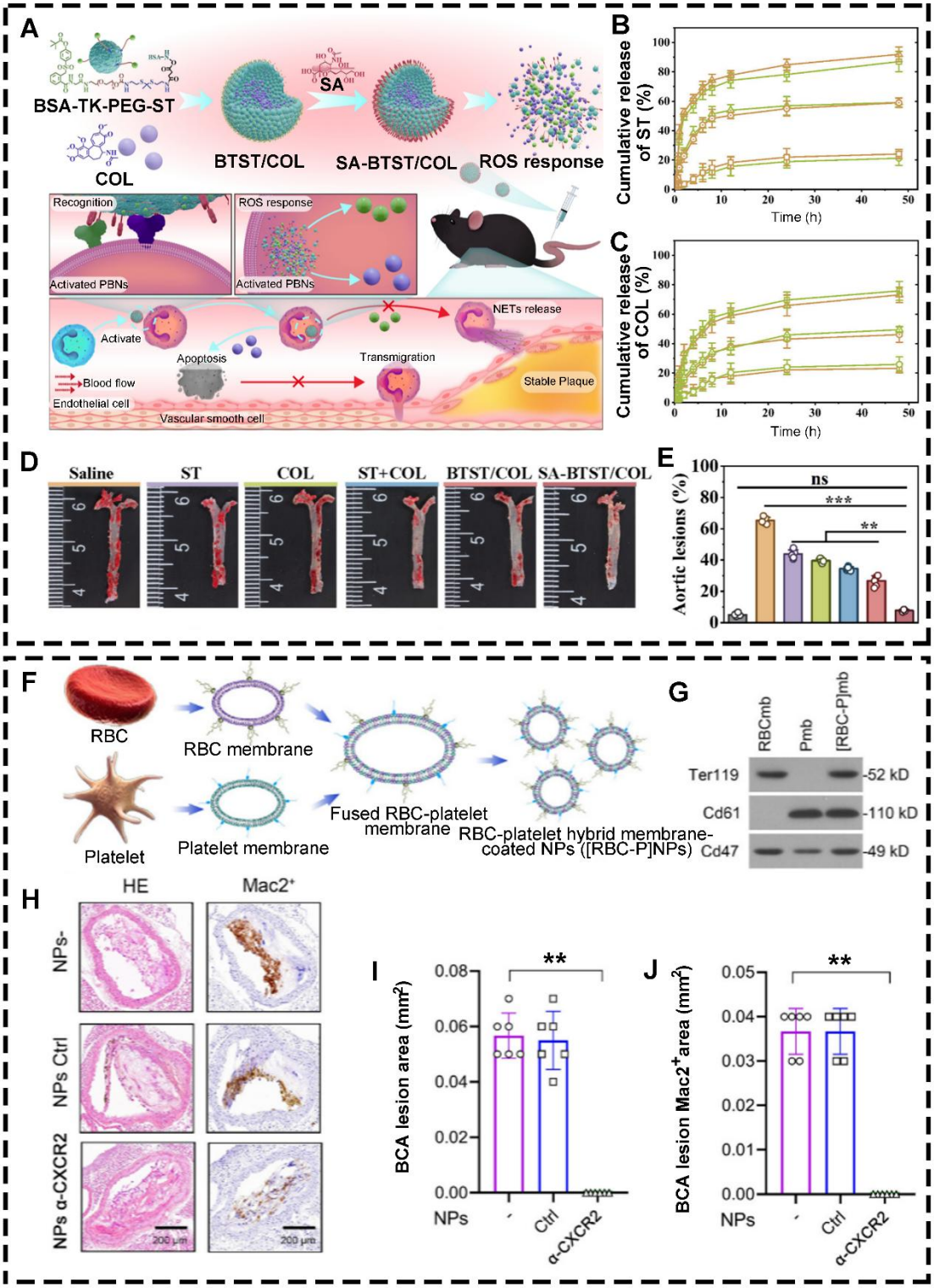


Fig. 15. (A) Schematic illustration of SA-BTST/Col for the treatment of atherosclerosis (AS) *via* inducing apoptosis of activated PBNs and inhibiting NET release. (B) Cumulative release profiles of ST from nanoparticles under different H_2O_2 concentrations. (C) Cumulative release profiles of COL from nanoparticles under

different H_2O_2 concentrations. (D) Oil Red O (ORO) staining of the brachiocephalic artery in atherosclerotic mice. (E) Quantitative analysis of the ORO-positive area in the brachiocephalic artery of atherosclerotic mice. (F) Schematic illustration of the preparation of [RBC-P] nanoparticles. (G) Immunoblot analysis of RBC membrane (RBCmb), platelet membrane (PM), and [RBC-P] membrane ([RBC-P]m) for the erythrocyte marker Ter119, platelet marker CD61, and the shared erythrocyte–platelet marker CD47. (H–J) Representative H&E and immunohistochemical staining images showing lesion size and Mac-2^+ area in the brachiocephalic artery (BCA), together with quantitative analyses. (A-E) Reproduced with permission [238]. Copyright 2025, Elsevier. (F-G) Reproduced with permission [239]. Copyright 2023, Elsevier.

4.1.5 Modulation of Immune Cell Polarization

Beyond simply suppressing immune cell infiltration or activity, a more sophisticated strategy for modulating the inflammatory microenvironment in CVDs centers on reprogramming immune cell polarization [240-242]. Most immune cells exhibit a high degree of plasticity, enabling them to dynamically adjust their functional phenotypes in response to local microenvironmental signals [243-245]. For instance, macrophages can polarize into the pro-inflammatory M1 phenotype that exacerbates damage, or they can transform into the anti-inflammatory M2 phenotype that promotes tissue repair [246-248]. Similarly, $CD4^+$ T cells can differentiate into subpopulations such as Th1, Th2, Th17, or Treg, thereby exerting antagonistic or complementary immune regulatory functions [249-250]. This section focuses on how nanomedicine can precisely regulate cell fate to promote reparative phenotypes and restore the immune balance of the cardiovascular microenvironment.

Dong *et al.*'s study exemplified nanomedicine-mediated reprogramming of the pathological cardiovascular microenvironment, demonstrating a biomimetic nanoparticle platform that concurrently reprograms macrophage polarization and normalizes dysregulated lipid metabolism (**Fig. 16A**) [251]. They designed liposomes

that were coated with the membrane of macrophages and modified with HA, for the co-delivery of rosuvastatin (RVS) and Hydroxysafflor yellow A (HSYA). This design utilized the HA to bind to the CD44 receptor on the surface of M1-type macrophages, ensuring the precise enrichment of the drugs at the plaque region. The co-loaded drugs could induce macrophages to transform from the pro-inflammatory M1 type to the repair M2 type, while significantly inhibiting foam cell formation. This effect was achieved by down-regulating the receptor CD36, thereby reducing lipid uptake and promoting autophagy-mediated lipid clearance (**Fig. 16B-D**). This nanosystem significantly reduced plaque burden in atherosclerotic mice and effectively enhanced plaque stability. This study demonstrated that engineered nanotechnology could precisely reprogram key cells, thereby promoting the transformation of the pathological microenvironment from pro-inflammatory to a dissociative state.

Fu *et al.* developed a novel "Trojan horse" strategy that achieved temporal control over the drug activity in atherosclerotic plaques (**Fig. 16E**) [252]. This strategy utilized circulating monocytes as a natural carrier to deliver the non-active nano-drug Citop-NM to the inflammatory lesion. This nanomedicine possessed an intelligent response mechanism, which could be specifically activated by high concentrations of ROS when monocytes differentiated into macrophages. This precise activation could effectively release therapeutic drugs, thereby reprogramming macrophages and reducing plaque burden (**Fig. 16F**). This strategy highlights the unique advantages of the stimulus-response system, which enables precise and targeted intervention of plaques by leveraging the inherent properties of immune cells. These advancements indicate that nanomedicine is moving in the direction of sensing microenvironmental signals, providing a translational strategy for restoring cardiovascular homeostasis.

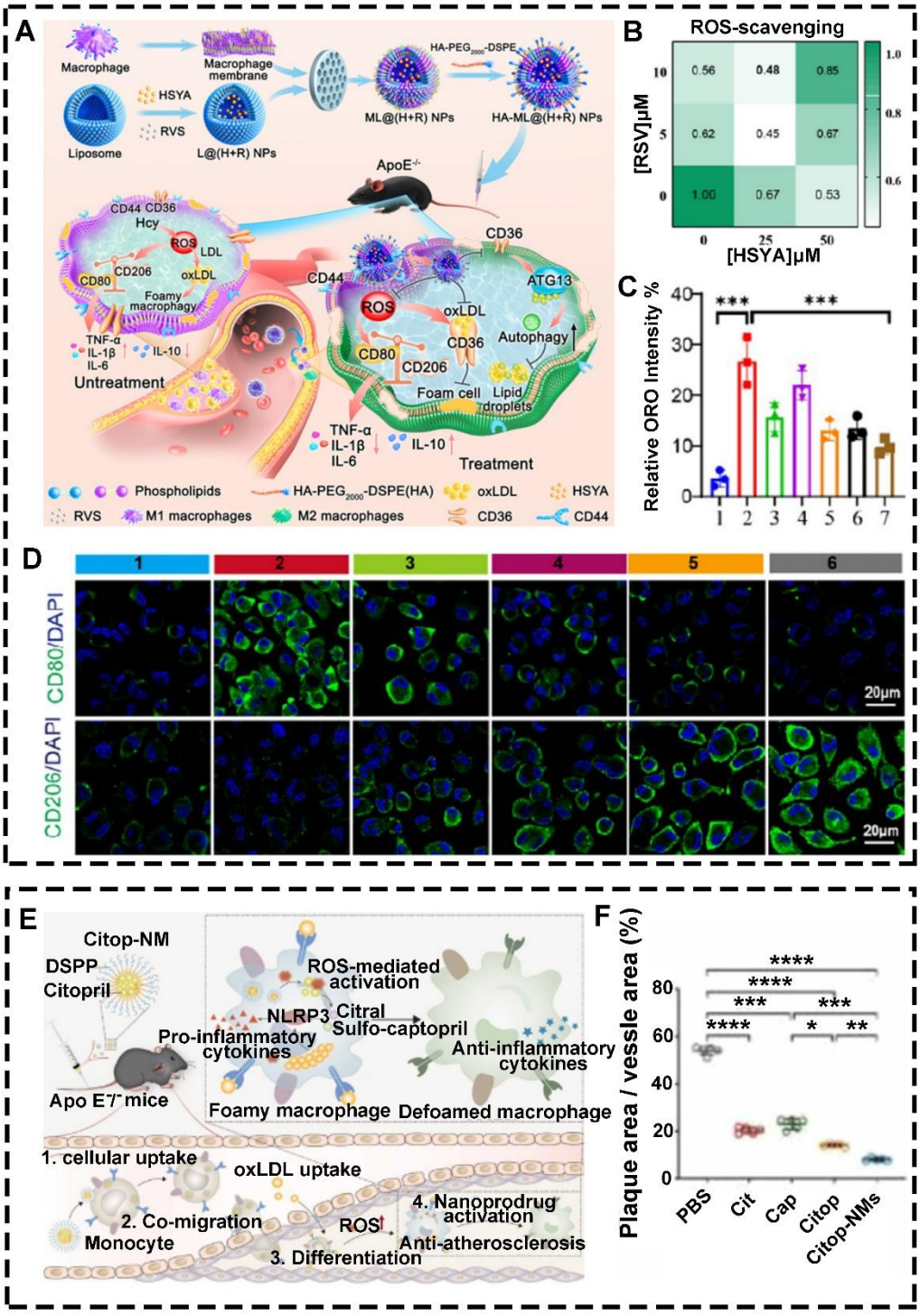


Fig. 16. (A) Schematic illustration of the preparation of HAML@(H+R) nanoparticles and their therapeutic strategy for Hcy-induced atherosclerosis. (B) Quantitative evaluation of ROS production in different treatment groups following pre-incubation. (C) Quantitative evaluation of foam cell formation in different treatment groups. (D) Immunofluorescence detection of CD80-positive and CD206-positive macrophages. (E) Schematic illustration of the activation of nanoprodrug precursors *via* monocyte

hitchhiking. (F) Comparative quantification of the plaque-to-vessel area ratios among different treatment groups. (A-D) Reproduced with permission [251]. Copyright 2025, American Chemical Society. (E-F) Reproduced with permission [252]. Copyright 2024, Elsevier.

4.2 Nanomedicines for Improving the Oxidative Stress Microenvironment

4.2.1 Antioxidants Delivery

As mentioned earlier, oxidative stress is a crucial factor driving cardiovascular microenvironmental lesions and plays a crucial role in inflammation and tissue damage [253-255]. Targeted antioxidant delivery, as a mechanism-based direct-effector strategy, has led to the development of various advanced nanodelivery systems [256, 257]. These engineered systems can effectively encapsulate unstable drugs, achieving their specific enrichment in regions with excessive ROS [258-260]. Nanocarriers, by virtue of their long circulation and targeting capabilities, significantly enhance the bioavailability and retention of antioxidants at the lesion site [261]. Nanoscale antioxidants restore the redox balance by eliminating excessive ROS, thereby alleviating oxidative damage and promoting endogenous repair [262-264].

In 2025, a research project prepared an all-fluorine-free MXene nanozyme Nb_2C-Pt@HA-PEG for the treatment of atherosclerosis [265]. The Nb_2C-Pt@HA-PEG dual enzyme exhibited high activity in simulating biological functions, efficiently eliminating ROS and inhibiting vascular inflammation under ultrasound stimulation (**Fig. 17A, B**). The results of animal experiments illustrated that the plaques of mice shrank by approximately 30% and the stability of the plaques was improved after injection of Nb_2C-Pt@HA-PEG (**Fig. 17C, D**). Significantly, this nanozyme demonstrated excellent biocompatibility, which could be effectively cleared by the body without causing obvious liver or kidney damage. This strategy embodies the core concept of nanomedicine, which is to effectively treat CVDs through restoring redox homeostasis.

This achievement was built upon the foundation of earlier research, the work of Liang *et al.* in 2023 provided an important example for this [266]. They developed a hydrogen peroxide scavenging biomimetic nanosystem (RPP-PU), whose core had a very strong responsiveness to high levels of ROS in the lesion. This nanosystem delivered the antioxidant drug probucol, which could prolong its circulation time in the body through encapsulating the red blood cell membrane. Additionally, RPP-PU employed the pathological microenvironment as the triggering mechanism, enabling to degrade and precisely release the drug upon reaching high ROS lesions. Animal experiments have confirmed that this system could efficiently eliminate ROS, thereby reducing plaque area and improving lipid metabolism. This research demonstrates the potential of responsive nanosystems in regulating oxidative stress, which provides a useful reference for future nanomedicine strategies.

To get rid of the reliance on polymer carriers, researchers have turned to exploring inorganic nanozymes with inherent therapeutic properties. For instance, Hu *et al*. successfully developed a multifunctional quadrupedal palladium hydride (PdH) nanozyme to scavenge ROS for the regression of atherosclerotic plaques (**Fig. 17E**) [267]. Notably, PdH nanozyme could eliminate ROS and release hydrogen to exert anti-inflammatory effects, which could also trigger autophagy in macrophages through the spiky structure (**Fig. 17F-H**). Furthermore, this method adopted an innovative *in vivo* delivery strategy, employing macrophages as "trojan horses" to actively migrate to the lesion plaques. This strategy embodied the regulatory concept of nanomedicine, effectively restoring redox balance and promoting microenvironment repair. Accordingly, this research demonstrates the advanced potential of nanomedicine for comprehensive regulation of the pathological microenvironment.

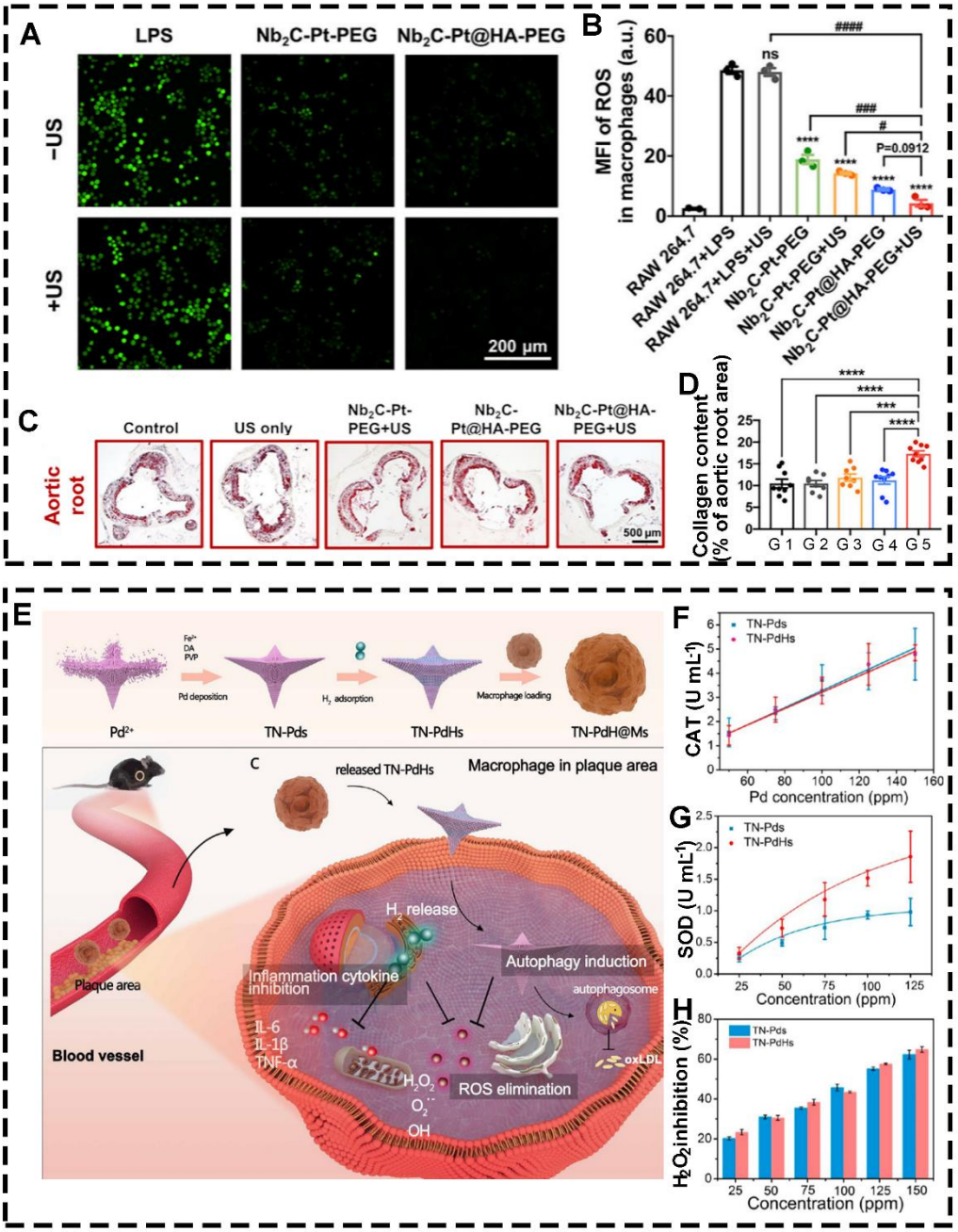


Fig. 17. (A) Representative confocal fluorescence images of intracellular ROS detected using the DCFH-DA assay. (B) Comparison of mean fluorescence intensity (MFI) in RAW 264.7 macrophages under different treatment conditions. (C) Representative images of ORO-stained aortic root sections from different treatment groups. (D) Relative quantification of collagen levels in different treatment groups. (E) Schematic illustration of the synthesis of TN-PDH@MS and its multiple therapeutic effects against atherosclerosis through autophagy-mediated synergistic treatment. (F) Comparison of CAT-like activity between TN-PDS and TN-PdHs. (G) SOD-like

activity of TN-PDS and TN-PdHs. (H) H_2O_2-removal efficiency of TN-PdHs. (A-D) Reproduced with permission [265]. Copyright 2025, Wiley-VCH. (E-H) Reproduced with permission [267]. Copyright 2022, American Chemical Society.

4.2.2 Nanomaterials with Antioxidant Activity

In addition to traditional drug encapsulation, the utilization of nanomaterials with inherent antioxidant activity has become an emerging therapeutic strategy [268-270]. This method relies on unique nanomaterials, which can catalyze the elimination of ROS on their own without relying on exogenous antioxidants [271-273]. These materials, known as "nanozymes", possess enzyme-like activity and can convert toxic ROS into harmless products to restore redox homeostasis [274-276]. Due to the fact that these materials can continuously take effect at the lesion site, they provide an efficient self-sustaining new strategy for reducing oxidative damage in the cardiovascular microenvironment [277-278].

For instance, a cobalt nanocatalyst with a biomimetic structure has been developed to treat aortic dissection by sustainably and efficiently scavenging pathological ROS **(Fig. 18A**) [279]. This nanocatalyst was fabricated by replacing zinc ions with cobalt ions in a zeolitic imidazolate framework, which created a Co-N4 coordination structure that was similar to the Fe-N4 structure of natural heme catalase. Theoretical calculations and experimental results demonstrated that the antioxidation reaction was catalyzed by the redox transition between hydroxocobalt (III) and oxo-hydroxocobalt (V), which facilitated a non-associated activation catalytic cycle. This biomimetic catalyst could effectively achieve the dissociation reaction of pathological hydrogen peroxide into oxygen and water. This nanocatalyst alleviated local oxidative stress, which could regulate the inflammatory microenvironment of the aorta by promoting the phenotypic transformation of macrophages. This process protected vascular smooth muscle cells from inflammatory damage, ultimately inhibiting the progression of aortic dissection. This study has fully demonstrated the core capability of nanomedicine in

precisely regulating the microenvironment in cardiovascular diseases. Moreover, this nanoplatform directly inhibited oxidative stress and blocked the ROS and inflammatory pathways, providing a reasonable technical framework of clinical treatment.

The concept of multi-enzyme cascade nanozyme has been widely adopted to address the complex pathological mechanisms of atherosclerosis. Researchers have successfully developed an integrated cascading nanozyme MSe1 through integrating selenium into the MOF framework [280]. This nanozyme possessed both SOD and GPx activities, enabling a cascade catalytic elimination of various ROS. This nanozyme was also designed to combat cellular aging, thereby inhibiting the pathological processes closely related to oxidative stress. In preclinical models, the MSe_1 nanozyme effectively attenuated the senescence of endothelial cells by protecting DNA from damage, weakening inflammation, and inhibited the formation of foam cells from macrophages and endothelial cells. This study demonstrates an integrated nanomedicine platform that simultaneously modulates multiple pathological microenvironmental dimensions, establishing multilevel intervention as a rational strategy for addressing multifactorial cardiovascular diseases.

Building on the concept of integrating therapeutic and diagnostic functions, carbon dot (CD) nanozymes have also been engineered as a theranostic platform for atherosclerosis (**Fig. 18B**) [281]. These CDs intrinsically possessed SOD-like antioxidant and anti-inflammatory activities, as well as capabilities for dual-modal photoacoustic and fluorescence imaging. To ensure precise delivery to the pathological microenvironment, these nanomedicines were surface-modified with the functional peptide CLIKKPF. This active targeting strategy enhanced the aggregation of the nanozymes at the lesion site, thereby maximizing the anti-inflammatory and therapeutic effects. This study presents a multifunctional nanoparticle that can simultaneously achieve the visualization and regulation of plaque oxidative stress. Collectively, this method represents an elegant strategy in nanomedicine-mediated therapy and provides a new solution for complex cardiovascular diseases.

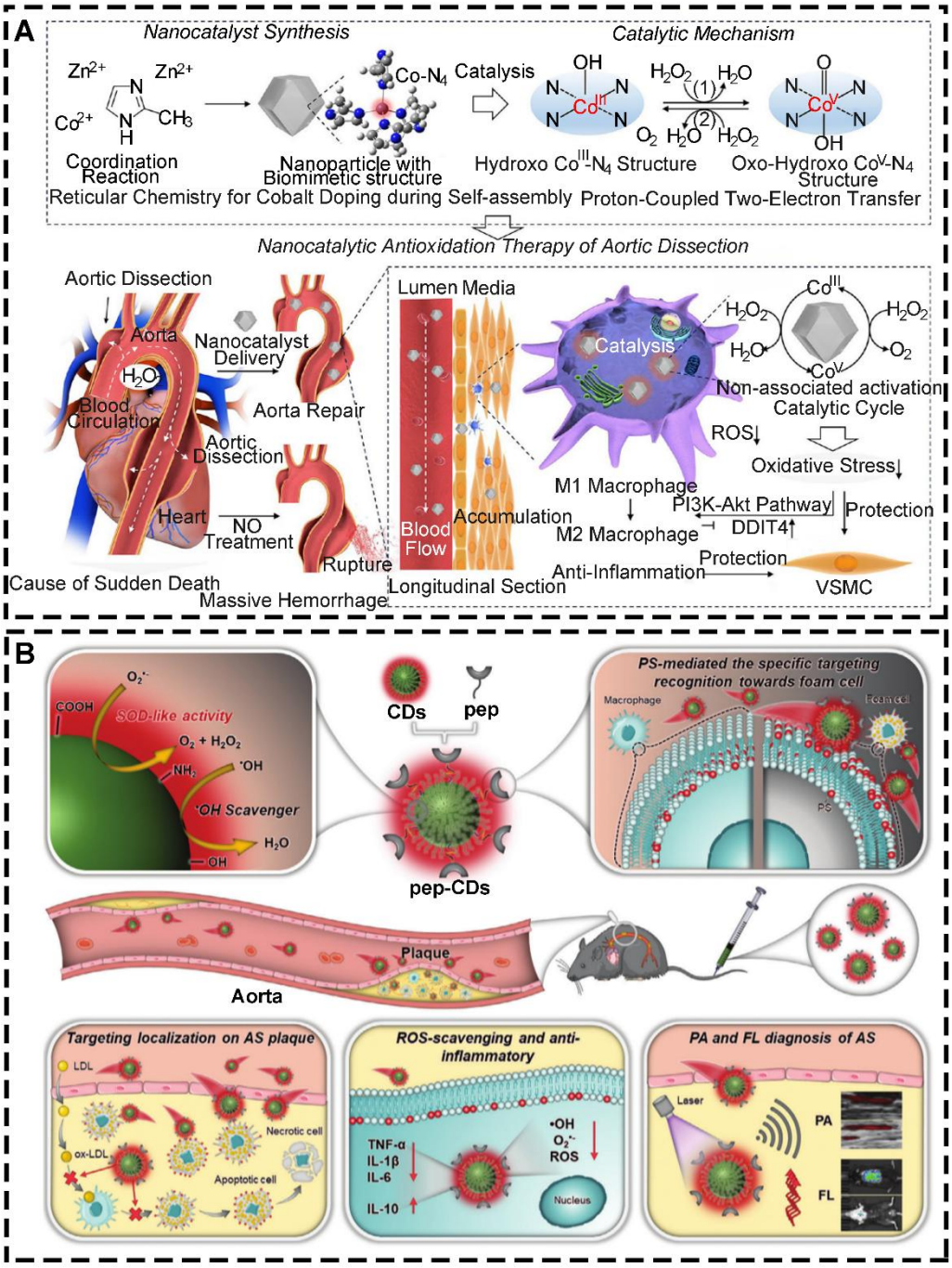


Fig. 18. (A) Schematic illustration of the synthesis and catalytic mechanism of Co-ZIF-8 nanocatalysts and their application in nanocatalytic antioxidative therapy for aortic dissection. (B) Schematic illustration of PEP-CDS with phosphatidylserine (PS)-targeting functionality. (A) Reproduced with permission [279]. Copyright 2024, American Chemical Society. (B) Reproduced with permission [281]. Copyright 2024, Wiley-VCH.

4.3 Nanomedicine for Regulating Extracellular Matrix Remodeling

In the cardiovascular pathological microenvironment, extracellular matrix (ECM) remodeling is a prominent factor determining disease progression and prognosis. Its dynamic changes have a profound impact on tissue structure, biomechanical integrity, and intercellular signal transduction [282-285]. This section systematically elaborates on the core strategies and mechanisms for regulating the extracellular matrix (ECM) homeostasis, thereby improving the therapeutic effect of cardiovascular treatment. The relevant nanomedicines mainly focus on three core dimensions: enzymatic degradation regulation, fibroblast transformation, and ion homeostasis restoration. This multi-level framework lays a solid foundation for the design of the next generation of intelligent cardiovascular nanomedicines.

For instance, Chen *et al.* developed an intelligent lipid nanoparticle system (GSL-NPs) to deliver the SercA2a gene for intervening in the lesions after myocardial infarction (**Fig. 19A**) [286]. This system precisely anchored to the infarction scar area utilizing collagen-binding peptides and simultaneously delivered the gene to local fibroblasts and cardiomyocytes (**Fig. 19B**). The expression of SercA2a in fibroblasts could block related signaling pathways, inhibiting cell activation and reducing collagen secretion. The supplementation of SercA2a in cardiomyocytes could restore calcium ion reuptake function, correct calcium overload and enhance myocardial contractility. The nanoparticles reduced fibrotic scars in the mouse model and significantly improved left ventricular ejection fraction (**Fig. 19C-E**). In summary, this study ingeniously utilized pathological ECM as a targeting anchor point, providing a highly promising gene nanocarrier for reversing ventricular remodeling after myocardial infarction.

In contrast to Chen *et al.*, who focused on inhibiting advanced fibrosis, excessive activation of MMPs in the early stage of myocardial infarction led to native ECM degradation, which was a primary cause of ventricular dilation and wall rupture. To address this, Sullivan *et al.* developed MMP-responsive polymeric micelles that

covalently incorporated small-molecule MMP inhibitors *via* hydrolyzable ester linkages

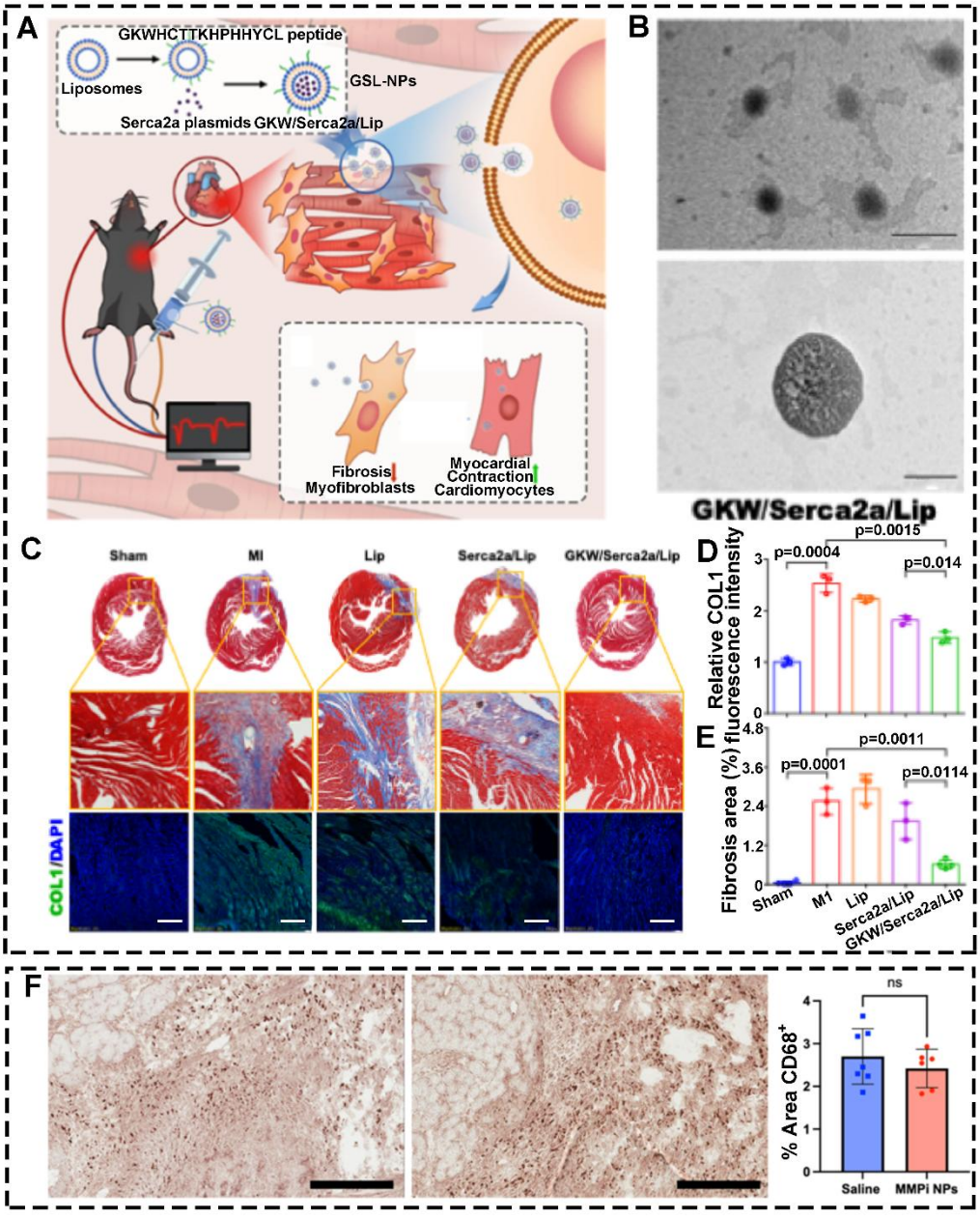


Fig. 19. (A) Schematic illustration of the design of GSL-NPs and their therapeutic effects in a mouse model of myocardial infarction. (B) Transmission electron microscopy (TEM) images of GSL-NPs at different magnifications (scale bars = 500 and 200 nm). (C) Representative Masson's trichrome staining and COL1 immunofluorescence images of the indicated groups (scale bar = 100 μm). (D, E) Quantitative analysis of scar area (D) and COL1 fluorescence intensity (E) based on

Masson's trichrome staining and immunofluorescence analysis. (F) Representative CD68 staining images of the infarcted myocardium at 7 days after injection in saline-treated and NP-treated hearts (scale bar = 200 μm), together with quantitative analysis of macrophage density. (A-E) Reproduced with permission [286]. Copyright 2024, Elsevier. (F) Reproduced with permission [287]. Copyright 2023, American Chemical Society.

in the core and displayed MMP-2/9-specific cleavable peptides on the surface (**Fig. 19F**) [287]. These micelles entered the myocardial tissue through vascular permeability after intravenous injection, which underwent surface peptide degradation under the action of local MMP-2/9. This enzymatic reaction resulted in a change in hydrophobicity and induced the micelles to aggregate *in situ* to form micrometer-sized precipitates. This *in situ* aggregation strategy enabled the drug to remain continuously in the infarcted lesions, which could not trigger microvascular obstruction or exacerbating cell infiltration. Subsequently, the drug was released *via* tissue esterase-mediated hydrolysis, efficiently inhibiting MMP catalytic activity to preserve native matrix architecture, while the macromolecular carrier significantly attenuated the cytotoxicity of free drugs. This work establishes an intervention strategy wherein pathological enzymes trigger drug aggregation and controlled release, providing a promising nanotechnology-based approach for precisely regulating excessive ECM degradation during the acute phase of myocardial infarction.

4.4 Strategies and Mechanisms for Nanomedicine to Target Angiogenesis and Vascular Repair

In the cardiovascular pathological microenvironment, angiogenesis and repair have dual functions and often exhibit functional disorders [288-290]. This section will explore the complex strategies and underlying mechanisms by which nanomedicines regulate angiogenesis and repair. We will investigate how these nanosystems stimulate

new blood vessel formation in ischemic tissues or inhibit harmful angiogenesis in atherosclerosis. For instance, researchers developed biocompatible nanomedicine

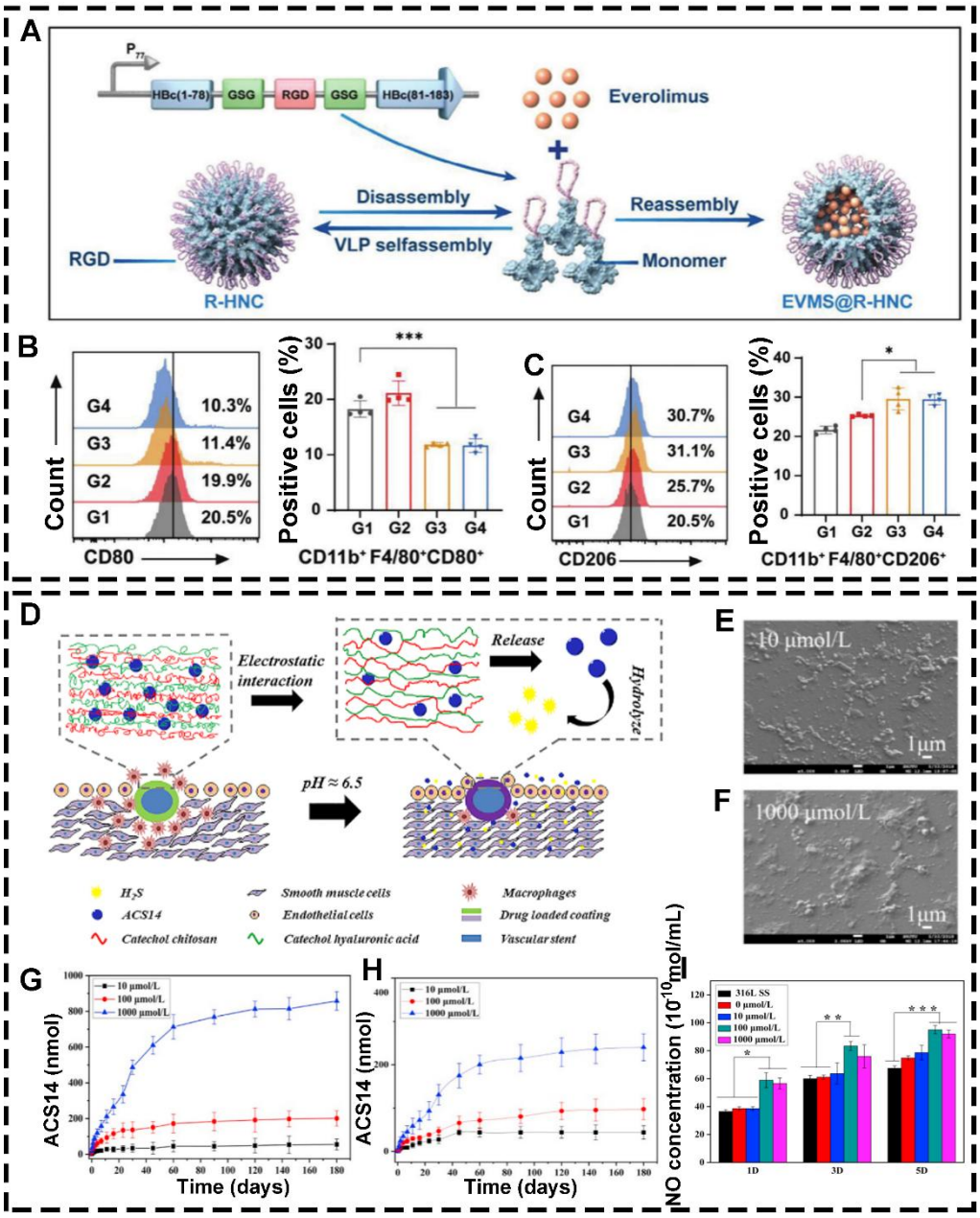


Fig. 20. (A) Schematic illustration of the synthesis process of EVMS@R-HNC. (B) Representative flow cytometry histograms and percentage quantification of $CD11b^+F4/80^+CD80^+$ M1 macrophages. (C) Flow cytometric analysis and quantification of $CD11b^+F4/80^+CD206^+$ M2 macrophages in different groups. (D) Schematic illustration of the smart coating releasing H_2S under mildly acidic conditions for vascular remodeling regulation. (E) Scanning electron microscopy (SEM) image of

the coating containing 10 μmol L^{-1} ACS14. (F) Scanning electron microscopy (SEM) image of the coating containing 1000 μmol L^{-1} ACS14. (G) Cumulative drug release from the loaded coating in phosphate-buffered saline (PBS, pH 6.5) over time. (H) Cumulative drug release from the loaded coating in phosphate-buffered saline (PBS, pH 7.4) over time. (I) Quantitative analysis of NO concentrations in endothelial cell culture media after incubation with different samples for 1, 3, and 5 days. (A-C) Reproduced with permission [291]. Copyright 2024, Wiley-VCH. (D-I) Reproduced with permission [292]. Copyright 2021, Elsevier.

EVMS@R-HNC for targeted treatment of abdominal aortic aneurysms by targeting critical pathological cells [291]. This nanomedicine was based on the results of single-cell analysis and employed RGD peptides to specifically target integrin receptors on M1 macrophages and smooth muscle cells (**Fig. 20B, C**). The targeted delivery of everolimus could inhibit macrophage polarization and block inflammatory responses, while maintaining the normal contraction function of smooth muscle cells. This integrated strategy indicated that nanomedicine could coordinate multiple cells and signaling pathways, thereby achieving comprehensive vascular repair and therapeutic intervention.

Similarly, nanomedicines can be designed to respond to the specific physicochemical characteristics of the pathological microenvironment, rather than targeting specific cell surface markers. For instance, an intelligent, pH-responsive coating has been developed to regulate vascular remodeling in coronary atherosclerosis (**Fig. 20D**) [292]. Coronary atherosclerotic lesions were known to have a low-pH, chronic inflammatory environment. To address this, a self-assembling film made of hyaluronic acid and chitosan was created to coat vascular stents (**Fig. 20E, F**). This film contained ACS14, an aspirin derivative that could release the therapeutic gas hydrogen sulfide (H_2S) gradually. The coating has been specially designed to enable the controlled release of the drug in the acidic microenvironment of the lesion (**Fig. 20G,**

H). This intelligent hydrogen sulfide release strategy was available to balance vascular function, effectively preventing complications such as restenosis within the stent (**Fig. 20I**). Overall, this strategy fully demonstrates the great potential of achieving precise treatment through regulating the pathological microenvironment.

4.5 Nanomedicines for Addressing Metabolic Disorders

4.5.1 Reduction of Lipoprotein Accumulation and Cholesterol Transport

Metabolic disorders are the main driving factors for the onset, progression and aggravation of various cardiovascular diseases [293-297]. This section focuses on the application of nanomedicines to correct metabolic disorders, aiming to reduce lipid deposition and restore cholesterol transport function. We have systematically reviewed various types of targeted nanotherapeutic strategies, including enhancing lipid clearance and promoting reverse cholesterol transport. These strategies also cover targeted delivery to foam cells and atherosclerotic plaques, thus providing new solutions for lipid metabolism regulation. For instance, Zhu *et al.* synthesized biomimetic nanoparticles MM@MTX with a surface covered by macrophage membranes for targeting atherosclerotic plaques (**Fig. 21A**) [298]. These nanoparticles were loaded with methotrexate and modified with cyclodextrin, and their membrane-coated property enabled active aggregation towards the inflammatory lesion. The cyclodextrin components could increase the solubility of cholesterol after reaching the target area, while the released drugs upregulated the expression of critical efflux factors (**Fig. 21B, C**). This dual-action approach not only inhibited the formation of foam cells by promoting reverse cholesterol transport but also reduced the plaque area and cholesterol crystal deposition, as demonstrated in mouse models of atherosclerosis (**Fig. 21D, E**). This platform demonstrates how nanomedicine can orchestrate microenvironmental modulation by synergizing biomimetic homing with localized metabolic intervention, simultaneously targeting the inflammation-lipid axis that drives atherosclerotic progression.

In a different approach focusing on both therapy and diagnostics, Wang *et al.* developed theranostic nanobubbles loaded with 2-Hydroxypropyl-beta-cyclodextrin (CDNBs) [299]. These nanobubbles were engineered to carry cyclodextrin, an FDA-approved drug known to dissolve cholesterol crystals, and could be triggered by ultrasound to release their therapeutic payload. Incorporating a near-infrared dye also allowed for both ultrasound and optical imaging. In a mouse model of atherosclerosis, these CDNBs were taken up by immune cells and passively accumulated in atherosclerotic lesions. The results of animal experiments have demonstrated that this targeted delivery significantly reduced the total area of plaques in the aorta and effectively lowered plasma cholesterol levels. This strategy combines passive targeting with ultrasound activation and can be used to regulate the lipid-rich microenvironment in atherosclerosis. Thus, these nanobubbles can promote the clearance of cholesterol crystals, thereby effectively inhibiting the inflammatory response triggered by the crystals.

In addition, Chen *et al.* designed a nanoplatform LPLCH that employed a "dual-channel" strategy to enhance reverse cholesterol transport (**Fig. 21F**) [300]. This system achieved active targeting of foam cells expressing CD44 in atherosclerotic plaques through a hyaluronic acid shell. Once internalized, the acidic environment within lysosomes triggered the disintegration of the nanoparticles (**Fig. 21G-J**). This process initiated a dual attack against cholesterol accumulation, as the nanoparticles not only captured crystals but also released LXR agonists. The LXR agonists then upregulated the ABCA1/G1 transporters, further promoting the active excretion of cholesterol from the foam cells (**Fig. 21K, L**). This nanoplatform not only inhibited the progression of the plaque but also demonstrated the ability to reverse the formed lesions. In summary, this method successfully achieved precise remodeling of the plaque microenvironment through a combination of physical removal and biological stimulation.

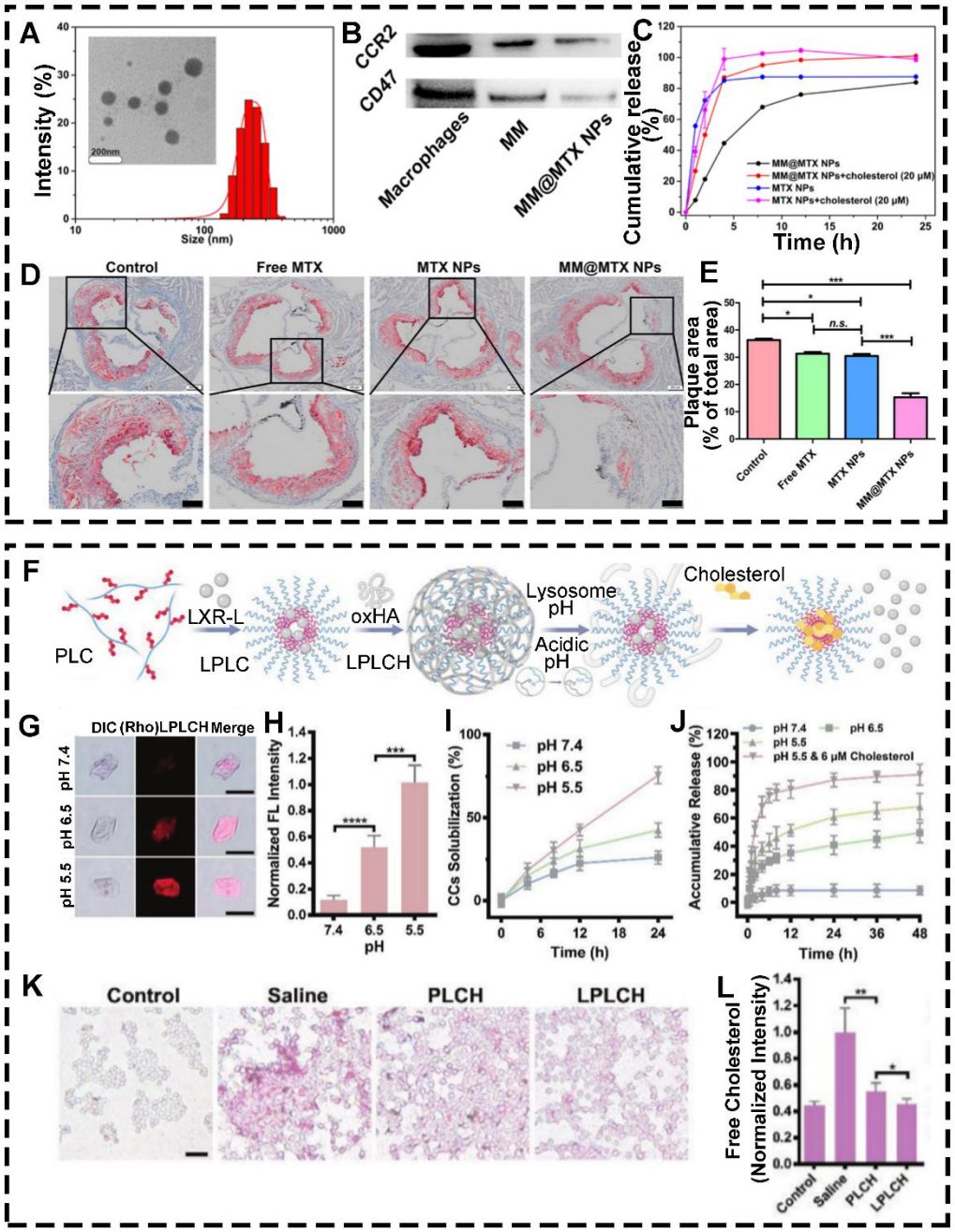


Fig. 21. (A) Transmission electron microscopy (TEM) image and particle size distribution of methotrexate nanoparticles measured by laser scattering spectroscopy. (B) Western blot analysis of CCR2 and CD47 expression under different treatment conditions. (C) *In vitro* methotrexate (MTX) release profiles from MTX nanoparticles and MM@MTX nanoparticles in phosphate-buffered saline (PBS, pH 7.4). (D) Representative Oil Red O-stained cross-sections of the aortic root from mice in different treatment groups. (E) Quantitative analysis of lipid deposition areas in aortic root cross-sections from five samples. (F) Schematic illustration of the preparation of

LPLCH with pH-responsive and lipid-loading capabilities. (G) Representative fluorescence microscopy images of rhodamine-labeled LPLCH interacting with CCS for 4 h under different pH conditions. (H) Quantitative analysis of the fluorescence intensity shown in (G). (I) Nanoparticle association with CCS after 12 h of incubation under different pH conditions. (J) In vitro release profiles of the LXR agonist under different pH conditions. (K) Representative optical microscopy images of foam cells subjected to different treatments. (L) Quantitative analysis of the fluorescence intensity shown in (K). (A-E) Reproduced with permission [298]. Copyright 2023, BMC (BioMed Central). (F-L) Reproduced with permission [300]. Copyright 2024, Wiley-VCH.

4.5.2 Inhibition of Foam Cell Formation

Foam cell formation, driven by the uncontrolled uptake of modified lipoproteins by macrophages, is a hallmark event in the initiation and progression of atherosclerosis, a major contributor to CVDs [301-305]. In this subsection, we will delve into the ingenious strategies and underlying mechanisms by which nanomedicines are being developed to effectively inhibit foam cell formation within the cardiovascular pathological microenvironment. We will investigate approaches such as inhibiting lipoprotein uptake and enhancing cholesterol efflux, so as to prevent lipoprotein modification and reduce its phagocytosis.

Although the aforementioned strategies focus on inhibiting the formation of foam cells, other techniques concentrate on directly removing foam cells. Segers *et al.* discovered that specific superparamagnetic iron oxide nanoparticles SPIOs accidentally induced apoptosis in foam cells (**Fig. 22A-D**) [306]. Mechanistic studies have confirmed that the oxidative stress induced by iron oxide triggered this apoptotic process, and antioxidant intervention could completely block this effect. While this procedure assisted in diminishing the cell load, it also underscored the safety of excessive cell apoptosis in advanced plaques. Studies have demonstrated that new

formulations ferumoxytol is non-cytotoxic, indicating that the surface characteristics of the nanoparticles are crucial for their biological effects (**Fig. 22E, F**).

Unlike inducing cell apoptosis, another restorative strategy focuses on regulating cholesterol metabolism to reverse the pathological phenotype of foam cells. Based on this concept, He *et al.* developed a "dual-channel" nanomedicine that specifically targeted macrophages to synergistically deliver siRNA and LXR ligands for treating atherosclerotic plaques [307]. This nanoplatform inhibited cholesterol uptake through silencing SR-A, which promoted cholesterol excretion through upregulating transport proteins. This synergistic strategy significantly reduced the intracellular cholesterol content, successfully reversing the formed atherosclerotic plaques in mouse models. Overall, this work demonstrates the great potential of nanomedicine in regulating the microenvironment, which can promote plaque regression by correcting metabolic disorders.

For example, Li *et al.* developed a "dual-cell therapy" nanoplatform to simultaneously target endothelial cells and macrophages for the precise therapy of atherosclerotic plaques (**Fig. 22G**) [308]. This nanoplatform was composed of a biomimetic lipid material encapsulating macrophage membrane, enabling immune evasion and actively targeting inflamed endothelial cells (**Fig. 22H, I**). Notably, this nanoplatform incorporated ROS-responsive linkers, ensuring the specific release of the dual drug payload in an oxidative stress environment (**Fig. 22J-L**). The released synergistic drugs could inhibit endothelial cell apoptosis, reduce macrophage lipid accumulation, and promote cholesterol excretion. This strategy proposes a comprehensive intervention approach that effectively remodels the atherosclerotic microenvironment closely related to plaque progression by simultaneously restoring the integrity of the endothelial barrier and alleviating macrophage lipid stress.

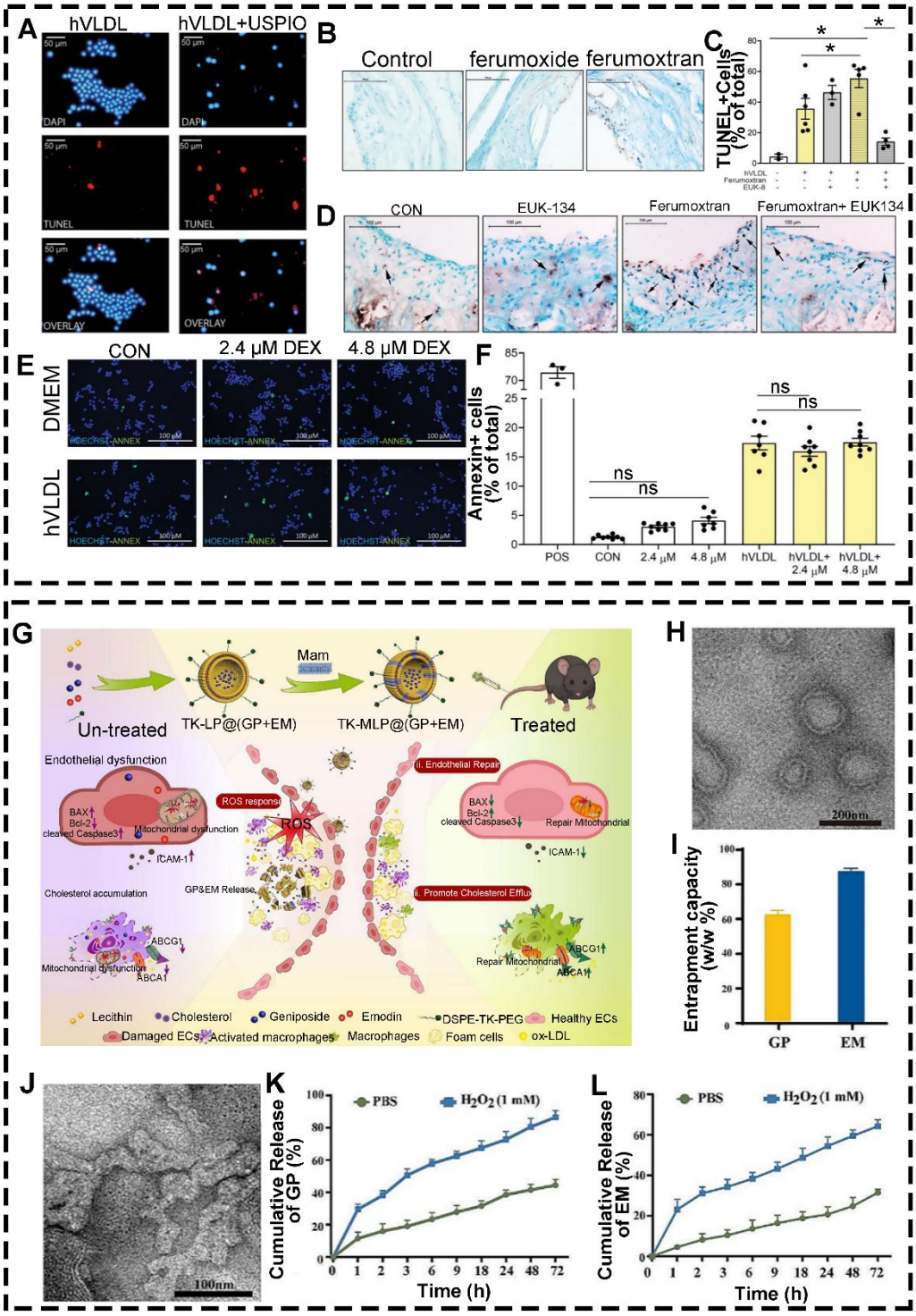


Fig. 22. (A) Representative fluorescence microscopy images of foam cells stained with DAPI and TUNEL following incubation with or without ferumoxtran for 1.5 h. (B) Representative TUNEL staining images of atherosclerotic plaques from mice in different treatment groups. (C) RAW264.7 cells converted into foam cells by human very low-density lipoprotein were incubated with ferumoxtran (dotted filling), inducing apoptosis. (D) Representative TUNEL staining images of atherosclerotic plaques from

low-density lipoprotein receptor-deficient mice under different treatment conditions. (E) Fluorescence microscopy images of RAW264.7 cells converted into foam cells following treatment with human very low-density lipoprotein for 1 h or normal lipid-containing medium (white bars) in the presence of 2.4 or 4.8 μM dextran or fresh DMEM. (F) Quantitative analysis of the fluorescence intensity shown in (E). (G) Schematic illustration of the preparation of TK-MLP@(GP+EM) nanoparticles and their therapeutic strategy for atherosclerosis. (H) Representative transmission electron microscopy (TEM) images of TK-MLP@(GP+EM) NPs. (I) Encapsulation efficiency of GP and EM in TK-MLP@(GP+EM) nanoparticles. (J) Representative TEM images of TK-MLP@(GP+EM) nanoparticles following exposure to 1 mM H_2O_2 for 4 h, showing their structural morphology. (K) In vitro release profiles of GP from nanoparticles in PBS and H_2O_2. (L) *In vitro* release profiles of EM from nanoparticles in PBS and H_2O_2. (A-F) Reproduced with permission [306]. Copyright 2022, Oxford University Press. (G-L) Reproduced with permission [308]. Copyright 2024, BMC (BioMed Central).

4.5.3 Promoting Cellular Lipid Efflux and Clearance of Dead Cells

Efficient lipid excretion and cell clearance are important mechanisms for maintaining cardiovascular homeostasis, helping to inhibit the occurrence of vascular diseases [309-312]. The obstruction of these metabolic processes leads to lipid accumulation, persistent pro-inflammatory signals, and unstable plaques in the pathological microenvironment [313-316]. This section systematically explores the nanomedicine strategies aimed at restoring physiological lipid homeostasis and alleviating inflammation. Specifically, we elaborate on three complementary mechanisms: mimicking lipid receptors, targeting delivery regulators, and stimulus-responsive carriers. In summary, these cutting-edge advancements highlight the core therapeutic value of nanotechnology in restoring lipid homeostasis and driving the resolution of inflammation.

For instance, Ding *et al.* developed biomimetic membrane-coated nanoparticles for synergistically treating atherosclerosis induced through homocysteine (**Fig. 23A-C**) [317]. To overcome the limitations of traditional drugs, the biomimetic nanoparticles combined the ability of atorvastatin to promote cholesterol excretion with the ability of astragaloside IV to scavenge ROS. Moreover, this system successfully achieved immune evasion and precise targeting of the CD44 receptor within the plaque through hybrid membrane modification and hyaluronic acid modification (**Fig. 23D**). Both *in vitro* and *in vivo* studies confirmed that this nanodrug effectively promoted cholesterol efflux and reduced lipid deposition by activating the LXRα-mediated ABCG1 and ABCA1/SR-B1 signaling pathway (**Fig. 23E, F**). Simultaneously, it activated Parkin-mediated autophagy, ameliorated mitochondrial damage, and inhibited ROS production. This research perfectly illustrates the core theme of nanomedicine-mediated regulation of the pathological microenvironment for the treatment of cardiovascular diseases. It employs an elegant nanoplatform to concurrently regulate two critical factors within the atherosclerotic pathological microenvironment-metabolic disorder (lipid accumulation) and oxidative stress, thereby restoring local microenvironmental homeostasis and effectively inhibiting disease progression.

Building upon the principle of targeting the atherosclerotic microenvironment, an innovative, carrier-free strategy developed by Chen *et al.* further refined this approach, addressing potential concerns about the toxicity and dose dependency associated with conventional nanocarriers [318]. They utilized the natural flavonoid luteolin to self-assemble into a nanomedicine termed “Dlut,” functionalizing its surface with oxidized dextran (oxDEX) to achieve the same precise targeting of the CD44 receptor on foam cells (**Fig. 23G**). The core ingenuity of this design lay in its dual-stimuli, “traceless” release mechanism; the Dlut nanoparticles remained stable in circulation but were engineered to completely disintegrate within the acidic and high-oxidative-stress microenvironment of the plaque, releasing the active drug precisely at the lesion without any residual carrier material. Transcriptomic profiling and subsequent

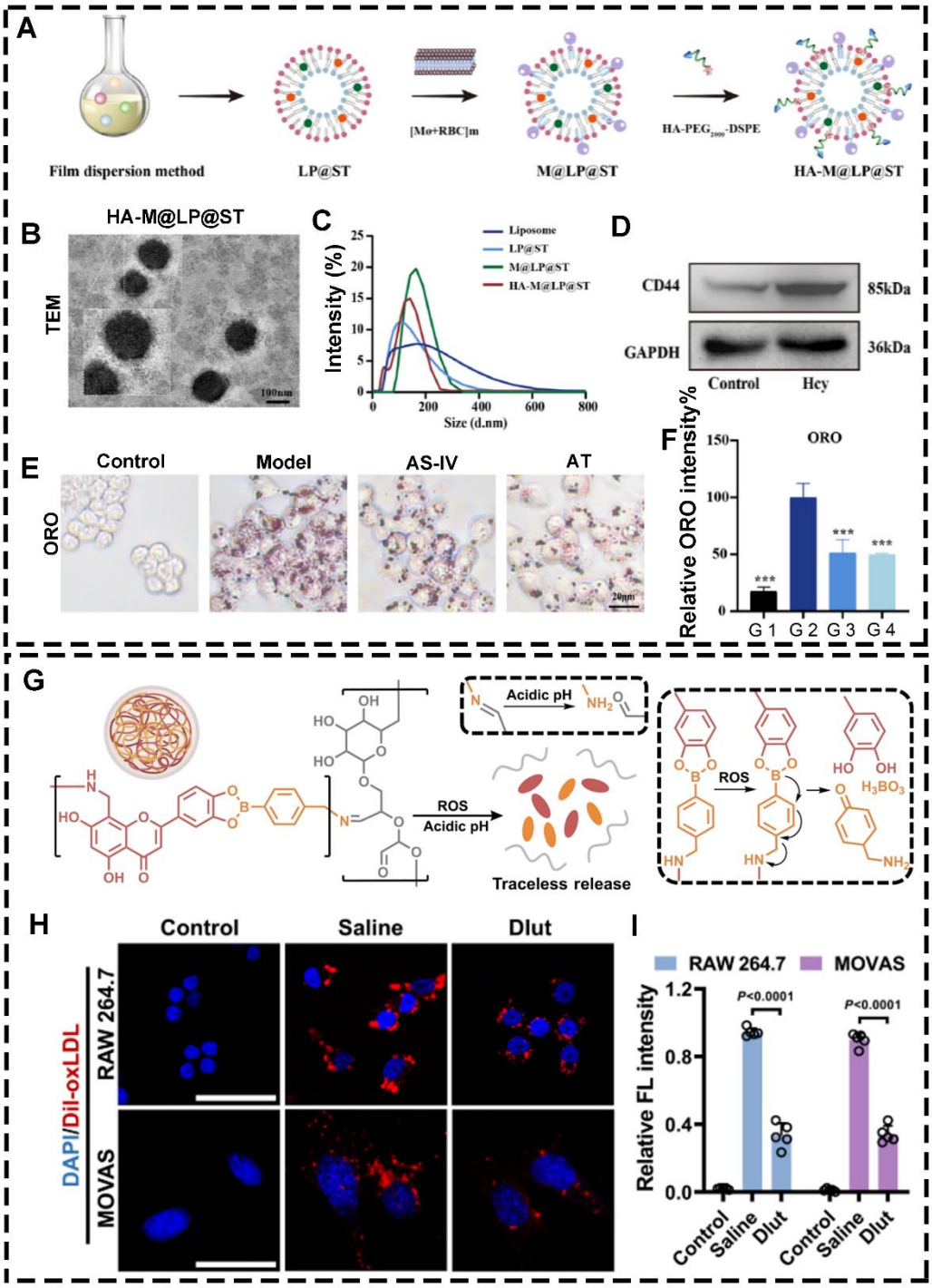


Fig. 23. (A) Schematic illustration of the synthesis process of HA-M@LP@ST. (B) Representative transmission electron microscopy (TEM) images of liposomes and HA-M@LP@ST. (C) Particle size distribution of HA-M@LP@ST determined by dynamic light scattering (DLS). (D) Western blot analysis of CD44 expression in macrophages following homocysteine stimulation. (E) Representative optical microscopy images of Oil Red O-stained macrophage-derived foam cells induced by oxLDL following

treatment with HA-M@LP@ST. (F) Quantitative analysis of Oil Red O (ORO) staining in oxLDL-induced macrophage-derived foam cells following treatment with HA-M@LP@ST. (G) Chemical structure of the flavonoid nanomedicine Dlut and schematic illustration of its degradation under acidic and ROS-rich conditions. (H) Representative images showing reduced residual DiI-oxLDL in cells following treatment with Dlut, indicating enhanced lipid efflux. (I) Quantitative analysis of the results shown in (H). (A-F) Reproduced with permission [317]. Copyright 2025, Elsevier. (G-I) Reproduced with permission [318]. Copyright 2025, Science Partner Journal.

validation revealed that Dlut's primary therapeutic mechanism was the acceleration of lipid efflux, accomplished by activating the LXR pathway to significantly upregulate the cholesterol transporters ABCA1 and ABCG1 (**Fig. 23H, I**). This study developed a self-delivering responsive nanoplatform targeting lipid metabolism of foam cells, providing a new strategy for the treatment of atherosclerosis by regulating the local metabolic microenvironment.

4.6 Cardiovascular Disease Therapy Based on Responsive Nanomaterials

Stimuli-responsive nanomedicines have emerged as a promising therapeutic platform, enabling to ingeniously exploit the unique pathological microenvironment of CVDs [319]. These nanosystems can achieve controlled drug release in response to pH values, ROS, or specific enzymes, thereby enhancing treatment specificity and reducing toxicity. The design of cleavable chemical bonds is crucial, because it can convert pathological signals into structural changes and controlled drug release. **Table 3** summarizes representative stimuli-responsive nanomedicines based on pathological triggers and response mechanisms to provide a brief overview. The following text will discuss pH, ROS, enzymes, and multi-response systems in detail, and will focus on their design principles and mechanisms.

Table 3. Stimulus-responsive polymer-based nanosystems and their application.

Polymers	Stimuli	Responsive linker	Theranostics application	Ref.
MSN@Ce/RSV-PT	pH	Schiff base	M1-to-M2 macrophage repolarization and synergistic anti-atherosclerosis therapy	[320]
miR-30d@ZIF-8	pH	Zn–N coordination bonds	Localized and sustained miR-30d delivery for myocardial I/R injury	[321]
si-Olfr2 NPs	ROS	o-DHLA	NIR-II photoacoustic imaging and si-Olfr2-mediated anti-atherosclerosis therapy	[326]
TPA-QO-B	ROS	Phenylboronic acid ester	FL/PA dual-modal imaging of atherosclerotic plaques	[327]
P-Mn/TI@mHSA	ROS	Thioketal (NHS-TK-NHS)	T1-weighted MRI and synergistic antioxidant–immunotherapy for atherosclerosis	[328]
PEG-peptide-CQDs	Enzyme (MMP-2/MMP-9)	MMP-2/MMP-9-sensitive substrate peptide	Urine-based fluorescent detection of early atherosclerosis and therapeutic monitoring	[335]
HALA@Ag_2S	Enzyme (hyaluronidase, HAL)	Hyaluronic acid (HA)	NIR-II imaging-guided photothermal therapy and programmable dual-drug delivery for atherosclerosis	[336]

Polymers	Stimuli	Responsive linker	Theranostics application	Ref.
Ac-βCD/RAP NPs	pH	Acetal groups	pH-responsive rapamycin delivery for macrophage modulation and anti-atherosclerosis therapy	[338]
Ox-βCD/RAP NPs	ROS	ROS-sensitive oxidizable groups	ROS-responsive rapamycin delivery for macrophage modulation and anti-atherosclerosis therapy	[338]
BIN	Enzyme (hyaluronidase), ROS and hypoxia	HA / ROS-responsive B-PDEA	Sequential multi-stage responsive gene delivery for myocardial ischemic tissue repair and revascularization	[339]

Note: MSN@Ce/RSV-PT: mesoporous silica nanoparticle (MSN) loaded with cerium ions and rosuvastatin (RSV); miR-30d@ZIF-8: miR-30d mimics were loaded by ZIF-8 nanoparticles; si-Olfr2 NPs: anti-Olfr2 small interfering RNA; TPA-QO-B: Phenylboronic ester-caged TPA-QO-OH probe; P-Mn/TI@mHSA: Platelet-conjugated Mn_3O_4 nanozyme/TRAF6 inhibitor-loaded mannose-modified human serum albumin nanoassemblies; PEG-peptide-CQDs: polyethylene glycol–peptide–carbon quantum dots; HALA@Ag_2S: Hyaluronic Acid-Lovastatin-Aspirin nanoassemblies loaded on Ag_2S quantum dots; Ac-βCD/RAP NPs: Rapamycin-loaded acetalated β-cyclodextrin; Ox-βCD/RAP NPs: Rapamycin-loaded ROS-sensitive β-cyclodextrin; BIN: bioinspired nanocobweb.

4.6.1 pH-Responsive Nanomedicines

Various cardiovascular lesions, including ischemic tissues, inflammatory atherosclerotic plaques, and myocardial infarction zones, can generate local acidic microenvironments of varying degrees. This acidic pH provides an important targeting

basis for pH-responsive drug delivery systems. pH-responsive nanomedicines contain degradable bonds or protonated groups, which can sense the acidic changes at the lesion site and regulate the drug release kinetics. This strategy is expected to enhance the drug utilization efficiency and reduce systemic adverse reactions, providing a new approach for precise cardiovascular nanotherapy. For example, Liu *et al.* developed a pH-responsive mesoporous silica nanosystem to load cerium nanozymes and the drug rosuvastatin for treating atherosclerosis (**Fig. 24A, B**) [320]. This nanozymes were encapsulated in a pH-sensitive Schiff base and could disintegrate in the acidic microenvironment of the plaque and trigger drug release (**Fig. 24C**). Furthermore, the cerium nanozymes with enzyme-like properties could effectively eliminate harmful ROS, exerting a synergistic antioxidant effect. This dual action synergistically inhibited inflammation and promoted macrophage polarization, ultimately reducing lipid deposition and delaying the progression of atherosclerosis (**Fig. 24D, E**). This pH-responsive strategy has a hierarchical effect, enabling to respond to both extracellular and intracellular acidic environments. Specifically, endosomal acidification triggered membrane instability and promotes the escape of cargo, thereby significantly increasing the bioavailability in the cytoplasm.

The researchers extended this strategy to the subcellular level, thus designing pH-responsive nanomaterials for overcoming intracellular barriers. For instance, Chen *et al.* fabricated an advanced ZIF-8 metal-organic framework nanoparticles to address myocardial ischemia-reperfusion injury. In this system, ZIF-8 metal-organic framework nanoparticles were employed to encapsulate miR-30d, a therapeutic microRNA (**Fig. 24F**) [321]. The ZIF-8 nanoparticles exhibited pH-sensitivity, remaining stable at physiological pH but rapidly disassembling in the acidic environment of endo/lysosomes after being internalized by cardiomyocytes. This pH-responsive degradation could trigger the proton sponge effect, enabling the carrier to escape from the lysosome and enter the cytoplasm to exert its anti-fibrotic function (**Fig. 24G, H**). Combined with a microneedle patch for localized and sustained

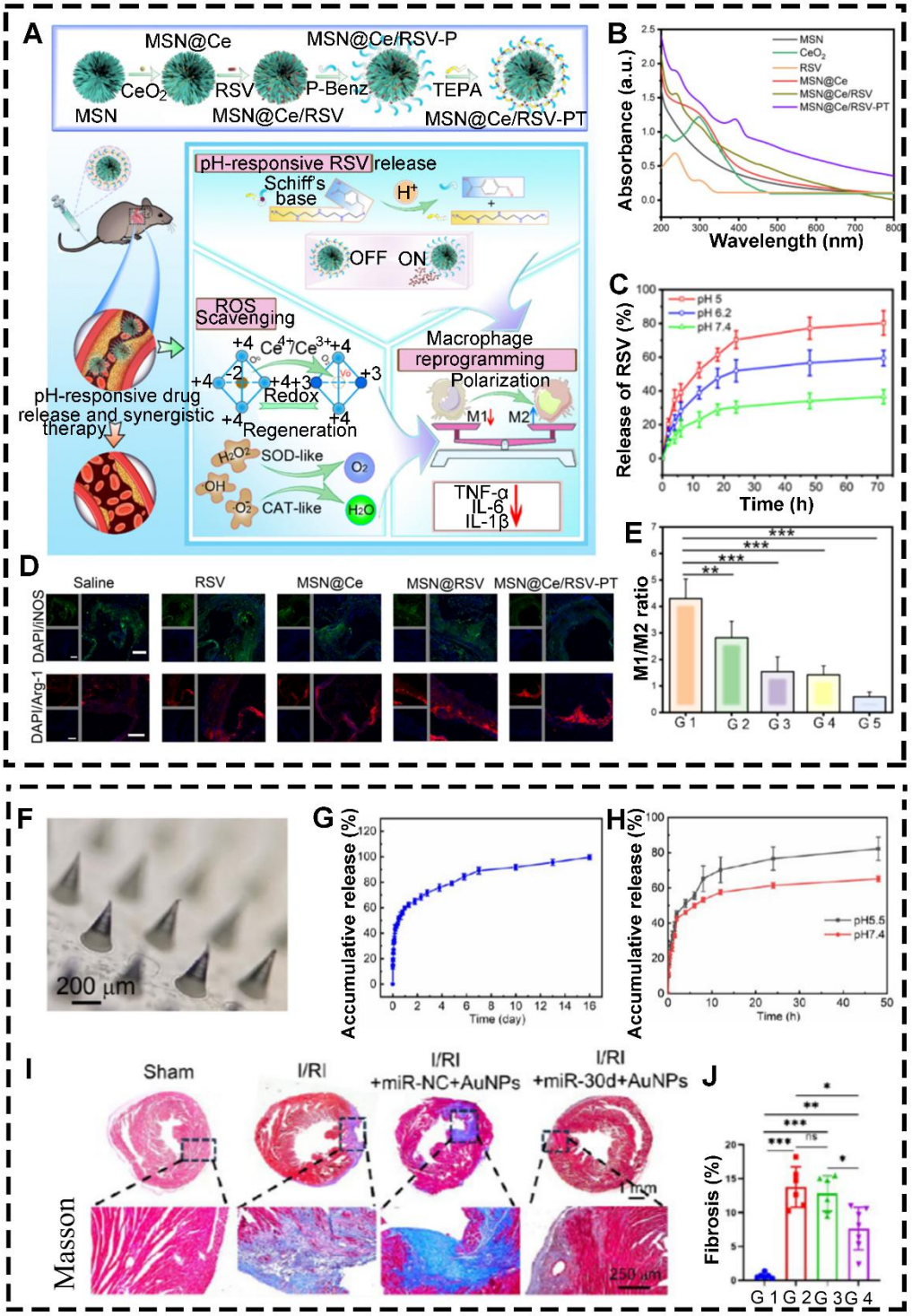


Fig. 24. (A) Schematic illustration of the construction and application of a pH-responsive MSN@Ce/RSV-PT nanoplatform designed to alleviate atherosclerosis by suppressing inflammation and oxidative stress. (B) UV–vis absorption spectra of different groups. (C) RSV release profiles from MSN@Ce/RSV-PT in solutions with different pH values. (D) Representative confocal laser scanning microscopy (CLSM) images showing the expression levels of iNOS and Arg-1 in aortic root tissues. (E)

Quantitative analysis of the M1/M2 (iNOS/Arg-1) ratio. (F) Representative microscopic image of the conductive microneedle patch. (G) Cumulative release profile of miR-30d-Cy3@ZIF-8 NPs from HAMA hydrogel in phosphate-buffered saline (PBS). (H) Simulated release profiles of miR-30d from miR-30d-Cy3@ZIF-8 NPs at pH 7.4 and 5.5. (I) Masson's trichrome staining of whole-heart sections and myocardial ischemic regions after 21 days of different treatments. (J) Quantitative analysis of the results shown in (I). (A-E) Reproduced with permission [320]. Copyright 2025, Elsevier. (F-J) Reproduced with permission [321]. Copyright 2024, American Chemical Society.

administration, this strategy demonstrated how pH-responsive nanomaterials could be designed to navigate the intracellular environment, ensuring the therapeutic cargo reaches its site of action (**Fig. 24I, J**). This approach highlights the versatility of pH-responsive nanomedicines in targeting different acidic compartments within the cardiovascular pathological microenvironment to achieve enhanced therapeutic efficacy.

4.6.2 ROS-Responsive Nanomedicines

ROS has a detrimental effect in the microenvironment of cardiovascular diseases, leading to oxidative stress and cell damage [322-325]. This section will explore ROS-responsive nanomedicines and analyze how they utilize the high concentration of ROS in the lesion area to achieve targeted intervention. We will focus on the design principle of ROS-sensitive bonds in nanoparticles to achieve precise and controllable drug release. This targeted delivery strategy not only enhances the therapeutic effect but also effectively avoids adverse reactions in non-targeted areas.

For instance, Ni *et al*. developed a ROS-responsive theranostics nanoplatform utilizing small interfering RNA to target the pro-inflammatory gene Olfr2 in macrophages for regressing atherosclerosis [326]. This nanosystem employed ROS-

responsive nanocarriers that could effectively encapsulate and deliver anti-Olfr2 siRNA. When reaching the high ROS microenvironment of the plaque, the nanocarriers would disintegrate and precisely release the therapeutic payload (**Fig. 25A-C**). This targeted delivery downregulated the expression of Olfr2 and inhibited the activation of the inflammasome and the secretion of pro-inflammatory factors (**Fig. 25D**). The nanoplatform also integrated near-infrared II-band photoacoustic imaging functionality, enabling high-resolution visualization of the lesion area. This study fully demonstrates the application potential of the ROS-responsive nanomedicine platform in regulating the inflammatory microenvironment and delaying plaque progression.

Some research strategies focus on diagnostic applications that employ ROS as a trigger to achieve early detection of plaques. For instance, Yu and colleagues prepared a ROS-responsive dual-modal fluorescence and photoacoustic imaging probe TPA-QO-B for the precise detection of atherosclerotic plaques [327]. This nanoprobe remained inactive in healthy tissues but could transform and activate the dual-modal signals in the high-ROS environment of plaques. Notably, the TPA-QO-B ingeniously combined the high sensitivity of fluorescence with the excellent tissue penetration depth of photoacoustic imaging. Overall, this nanoprobe can clearly visualize early plaques, highlighting the great potential for developing highly sensitive diagnostic tools based on ROS responses.

Additionally, Li *et al.* developed a ROS-responsive platelet-targeted theranostics nanoplatform, demonstrating a multi-stage adaptive delivery mechanism (**Fig. 25E**) [328]. This nanosystem utilized platelets as a natural carrier to simultaneously deliver manganese-based nanocatalysts and TRAF6 inhibitors to target atherosclerotic lesions. When entering the high ROS microenvironment of the plaque, the breakage of the connection chain released active protein fragments that could be taken up by macrophages. The catalyst was responsible for eliminating ROS to alleviate oxidative stress inside the cells, while the inhibitor regulated the immune response by blocking cell activation. The released manganese ions enhanced the magnetic resonance imaging

signal, thereby endowing this nanoplatform with powerful diagnostic imaging capabilities. This multi-functional design combines natural targeting with stimulus-responsive delivery, providing a new framework for the development of cardiovascular nanomedicines.

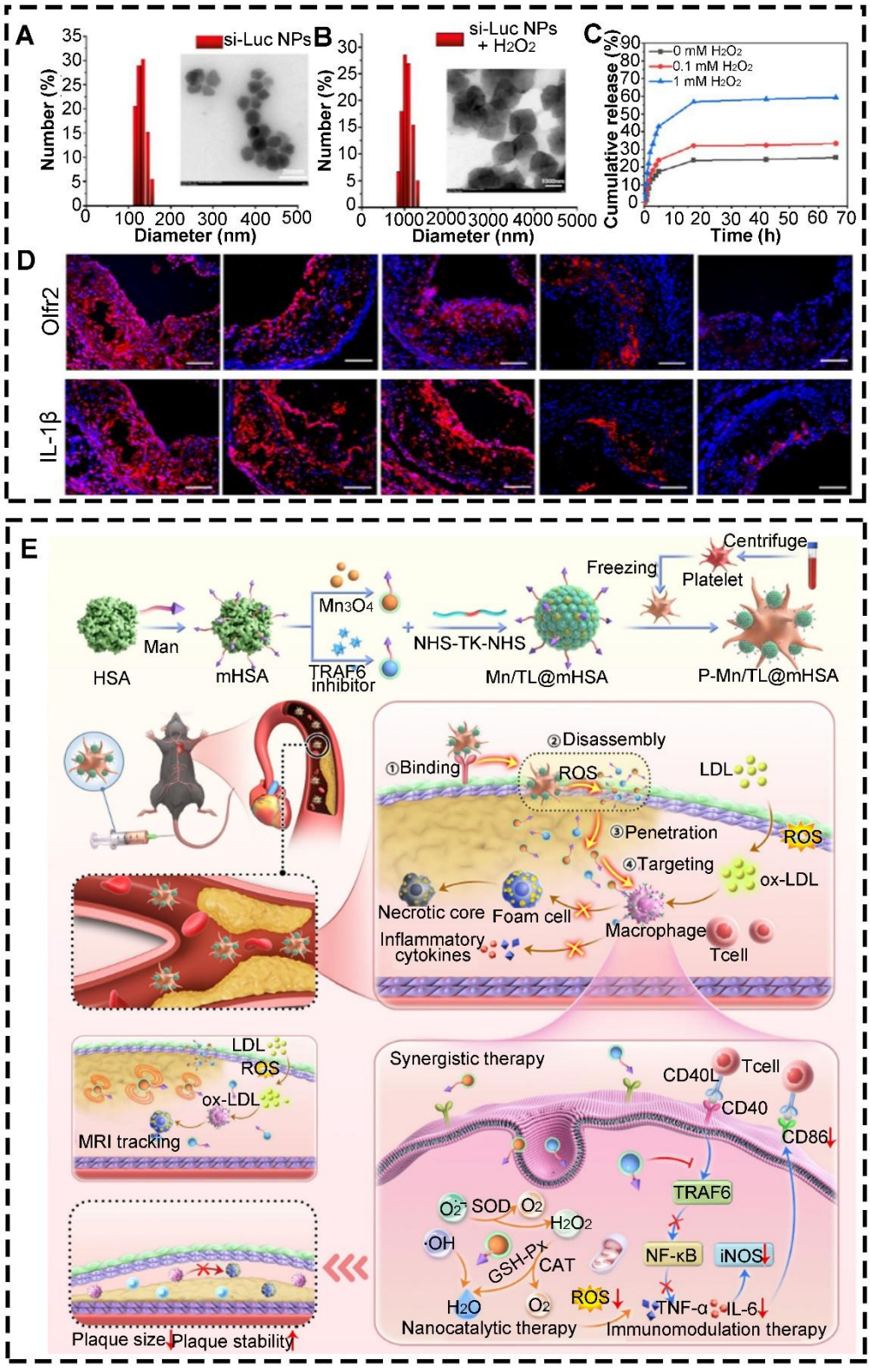


Fig. 25. (A) Dynamic light scattering (DLS) and transmission electron microscopy (TEM) of si-Luc nanoparticles. (B) DLS profile and TEM image of si-Luc nanoparticles after 2 min of incubation with 10 mM H_2O_2. (C) Comparative release profiles of FITC from o-DHL nanoparticles in the presence or absence of H_2O_2. (D) Immunofluorescence analysis of Olfr2 and IL-1β co-stained with Mac-2 in aortic root sections from $ApoE^{-/-}$ mice subjected to different treatments. (E) Schematic illustration of a programmable platelet-derived nanoplatform integrating active targeting, magnetic resonance imaging (MRI)-based diagnosis, and immunomodulatory functions for the treatment of atherosclerosis. (A-D) Reproduced with permission [326]. Copyright 2024, American Chemical Society. (E) Reproduced with permission [328]. Copyright 2024, American Chemical Society.

4.6.3 Enzyme-Responsive Nanomedicines

The abnormal expression of certain enzymes in the cardiovascular pathological microenvironment plays a crucial role in the progression of the disease [329-334]. This subsection will delve into enzyme-responsive nanomedicines and elucidate the mechanism by which intelligent nanosystems utilize enzymatic characteristics to achieve precise intervention. We will focus on discussing the design of enzyme-cleavable linker nanoparticles to achieve on-demand drug release at the lesion site. This precise targeting strategy effectively maximizes therapeutic benefits, effectively avoiding systemic adverse reactions.

For example, Wu *et al.* developed synthetic nanosensors that could effectively achieve early detection of atherosclerotic lesions. They employed carbon quantum dots as fluorescent probes and connected the peptide substrate that could be cleaved by MMP enzymes to the carrier (**Fig. 26A, B**) [335]. This structure was specially designed to specifically target VCAM-1, ensuring that the drug can effectively accumulate at the atherosclerotic lesion. Upon cleavage by the overexpressed MMPs in the plaques, the CQDs were released, cleared by the kidneys, and excreted in the urine (**Fig. 26C**). This

study enabled to conduct a simple and minimally invasive urine test, whose fluorescence intensity could directly reflect the enzyme activity in the atherosclerotic lesion and enable early diagnosis. This platform demonstrates nanomaterial-based detection of enzymatic dysregulation in cardiovascular disease, converting pathological enzyme activity into non-invasive diagnostic signals and exemplifying stimulus-responsive nanomedicine for cardiovascular applications.

Expanding on this concept from diagnostics to therapeutics, Liang *et al.* developed an intelligent, hyaluronidase-responsive nanoplatform HALA@Ag_2S for the multimodal treatment of atherosclerosis (**Fig. 26D, E**) [336]. This nanoplatform HALA@Ag_2S employed a hyaluronic acid (HA) matrix, which could be specifically degraded by the overexpressed hyaluronidase in the plaque. The HA matrix not only simultaneously loaded aspirin and lovastatin, but also incorporated Ag_2S quantum dots for near-infrared II region imaging and photothermal therapy. Moreover, the HA component actively targeted activated macrophages in the plaque through the CD44 receptor. Once at the lesion, the enzyme-induced nanoplatform disintegration would trigger the local controlled release of the two drugs. Accordingly, the integrated photothermal therapy exhibited a synergistic therapeutic effect, not only achieving local anti-inflammatory effects but also enhancing drug release and plaque permeability. This enzyme-responsive platform integrates dual-drug delivery with photothermal therapy, exploiting pathological enzymatic activity to trigger synergistic therapeutic effects and providing a strategy for cardiovascular disease intervention.

In addition to triggering the release of the payload, enzyme sensitivity can also drive adaptive size changes to break through the dense tissue barrier. For example, Liang *et al.* designed a tissue CTSK-responsive nanoplatform (PDE@Mn_3O_4/SIM), which significantly shrank in size after CTSK was overexpressed on the surface [337]. This enabled it to effectively overcome the physical space obstruction of the fibrous cap and penetrate deep-seated lesion macrophages. This size-reducing design, combined with the synergistic ROS scavenging effect of ultra-small Mn_3O_4 nanozymes and

simvastatin-mediated cholesterol efflux, is significantly superior to static, non-reducible nanocarriers in reducing the necrotic core and stabilizing vulnerable plaques.

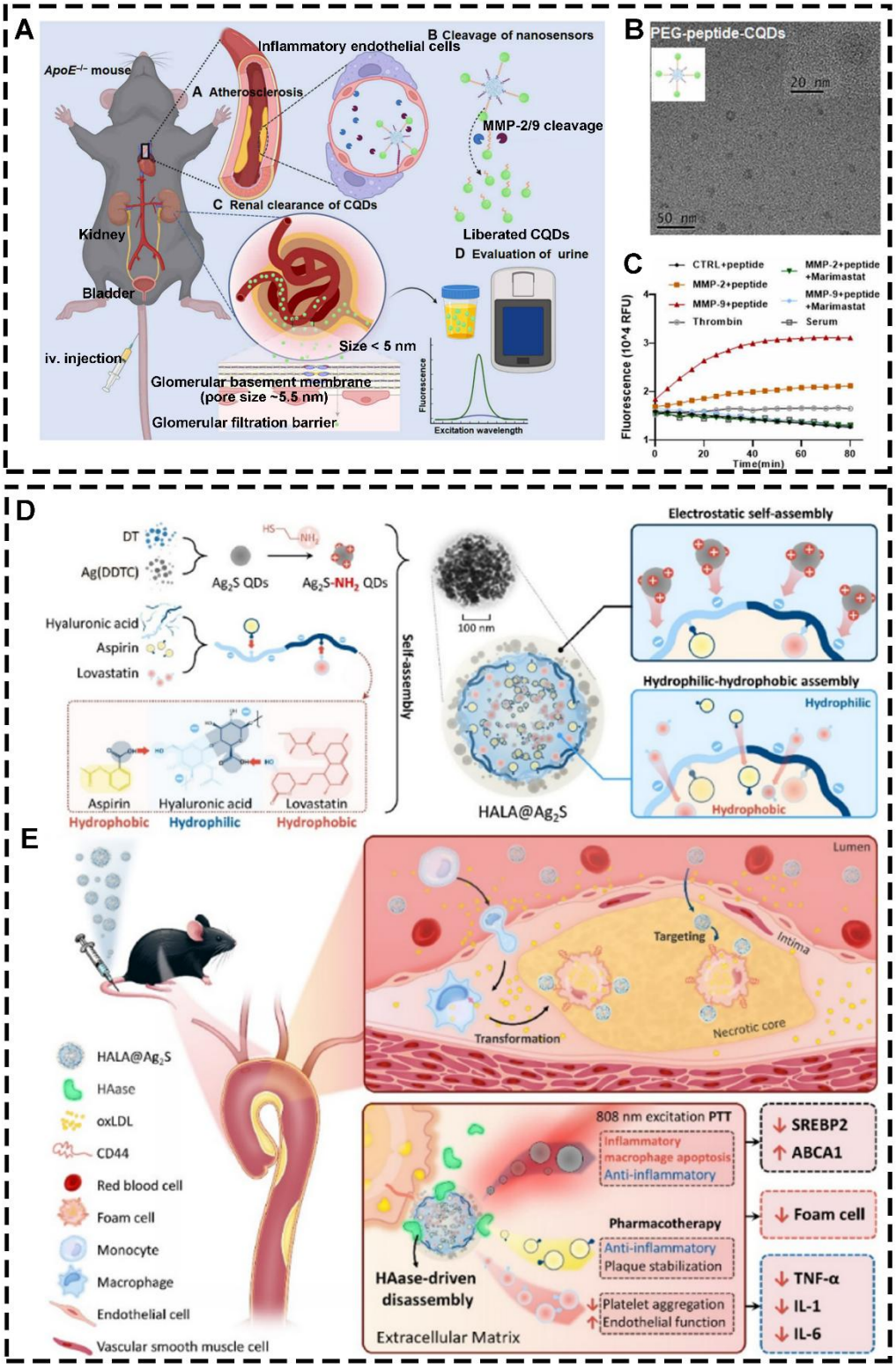


Fig. 26. (A) Schematic illustration of the PPCs nanosensor for MMP-responsive detection of atherosclerotic lesions in ApoE$^{-/-}$ mice and urinary fluorescence-based

signal detection. (B) Representative transmission electron microscopy (TEM) image of PEG-peptide-CQDs. (C) Representative fluorescence activation profiles of peptide substrates following treatment with the recombinase, demonstrating rapid fluorescence increases for specific protease–substrate pairs. (D) Schematic illustration of the development and fabrication of Hala@Ag_2S nanoassemblies. (E) Schematic illustration of the therapeutic mechanism within atherosclerotic plaques. (A-D) Reproduced with permission [335]. Copyright 2025, American Association for the Advancement of Science. (E) Reproduced with permission [336]. Copyright 2025, Elsevier.

4.6.4 Multi-Responsive Nanoplatforms

While single-stimuli responsive nanomedicines offer significant advantages in targeted drug delivery, the complex and heterogeneous nature of the cardiovascular pathological microenvironment often involves the simultaneous dysregulation of multiple biological cues, such as abnormal pH, elevated ROS, and overexpression of specific enzymes. This section will delve into the cutting-edge field of multi-responsive nanosystems, further elucidating their synergistic mechanisms that are sensitive to various pathological stimuli. We will explore the rational design of such intelligent systems, which demonstrates their advantage of achieving precise targeting through the coordinated response of multiple signals. This complex response mechanism ensures that the therapeutic approach is more precise and effective, which also minimizes adverse effects outside the target area.

For instance, Dou *et al.* developed a pH and ROS multi-responsive nanoplatform Ac-bCD and Ox-bCD for the efficient treatment of atherosclerosis (**Fig. 27A**) [338]. They synthesized pH and ROS multi-responsive cyclodextrin derivatives and prepared them into nanoparticles to deliver rapamycin. Among them, the Ac-bCD nanoparticles could release drugs rapidly in an acidic environment, while the Ox-bCD particles could specifically degrade under excessive H_2O_2 conditions (**Fig. 27B, C**). These two responsive nanomedicines demonstrated excellent efficacy in animal models,

effectively delaying plaque progression and enhancing stability (**Fig. 27D**). Collectively, this study fully demonstrated the therapeutic advantages of nanomaterials designed for different pathological triggers.

Traditional systems only respond to the static characteristics of the pathological environment, while more advanced solutions program nanoparticles to respond sequentially during different disease stages. A brilliant execution of this concept was the "cobweb-inspired" nanosystem developed by Ding *et al.*, which featured a HA network ensnaring core nanoparticles composed of a ROS-responsive polymer and a hypoxia- sensitive VEGF-expressing plasmid (**Fig. 27E**) [339]. This design enabled a programmed therapeutic cascade: first, elevated hyaluronidase in the extracellular matrix degraded the HA "cobweb," releasing the nanoparticles for cellular uptake. Excessive ROS would trigger the degradation of the polymers once inside the cells, releasing the plasmids and consuming the ROS to alleviate oxidative stress. The subsequent local hypoxic environment could activate the released plasmids and promote VEGF expression, thereby effectively promoting local vascular regeneration. This strategy highlights the unique advantages of responsive nanomedicines in different pathological stages, which provides an innovative paradigm for the intervention of complex CVDs.

The efficacy of cardiovascular nanomedicines is not only determined by molecular targets, but is also constrained by multiple physiological processes such as cell uptake, circulation kinetics, and off-target clearance. Active targeting and biomimetic camouflage can enhance cell recognition or prolong circulation time, but *in vitro* advantages often cannot be directly translated into high accumulation rates at the lesion site. Similarly, stimulus-responsive systems can achieve on-demand drug release, but their actual effects highly depend on the specificity and heterogeneity of pathological microenvironment signals. Therefore, we must not solely rely on a single material design characteristic as the criterion when evaluating the clinical translational potential

of nanomedicines, but must systematically take into account targeting efficiency, pharmacokinetic behavior, and long-term safety.

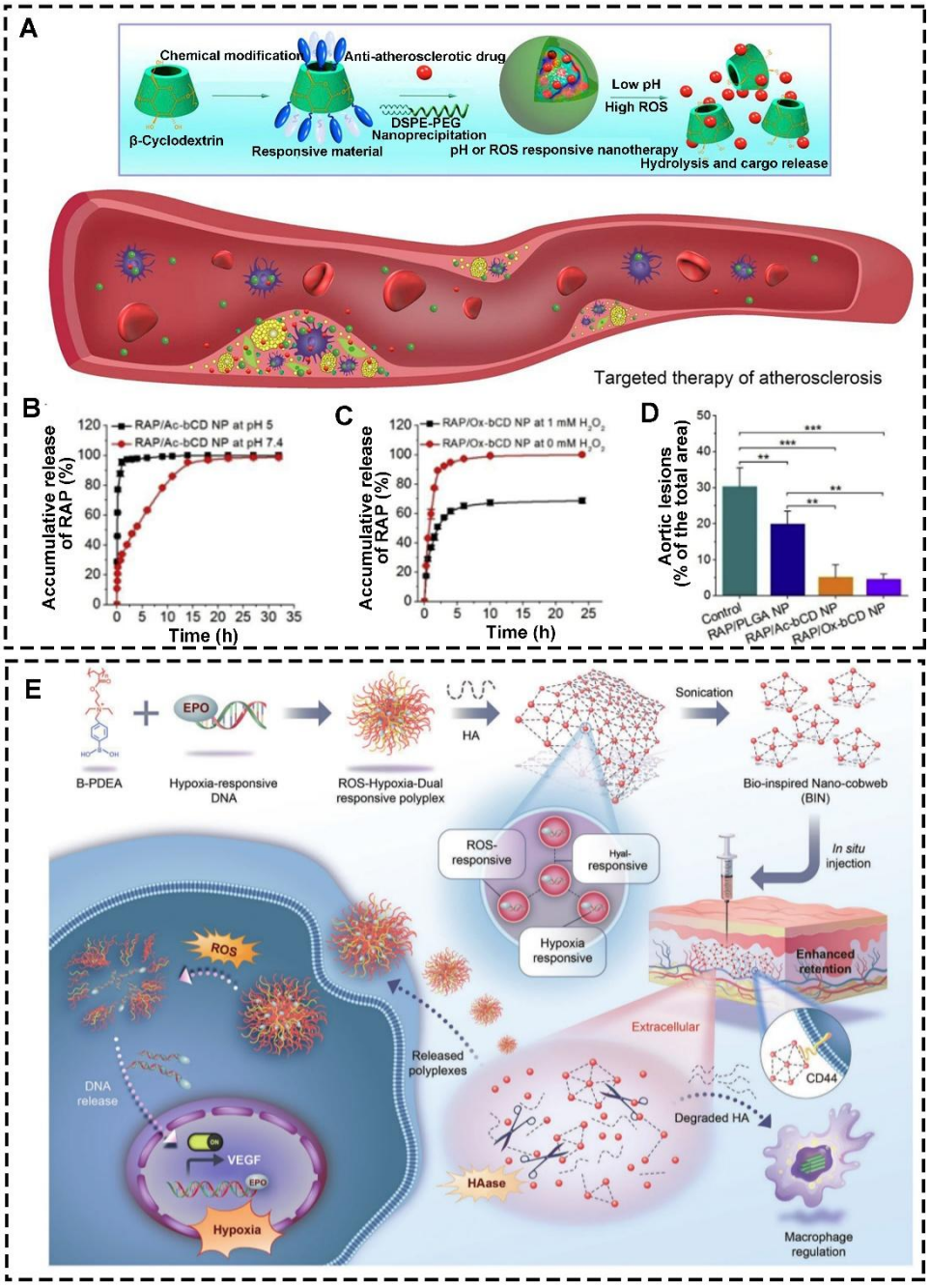


Fig. 27. (A) Schematic illustration of stimuli-responsive β-cyclodextrin-based nanomedicine for targeted therapy of atherosclerosis. *In vitro* cumulative RAP release profiles from (B) RAP/Ac-bCD NPs in buffers at various pH values, and (C) RAP/Ox-bCD NPs in the presence of gradient H_2O_2 concentrations. (D) Quantitative evaluation of the aortic plaque coverage (%). (E) Schematic illustration of the preparation of a spider silk-inspired adhesive nanosystem and its mechanism of action in ischemic tissue

repair. (A-D) Reproduced with permission [338]. Copyright 2017, Elsevier. (E) Reproduced with permission [339]. Copyright 2023, Wiley-VCH.

5. Challenges and Future Prospects

The microenvironment framework proposed in this paper represents a paradigm shift, evolving from simple physical and chemical design to the construction of customized pathological features. Moreover, the comprehensive integration of preclinical animal experiments is crucial for bridging the gap between mechanism verification and translational research. This is not only a key prerequisite for systematically evaluating the *in vivo* behavior of nanomedicines, but also provides a novel paradigm for cardiovascular treatment that combines targeting and clear mechanisms. Through the utilization of pathological signals such as tissue acidosis and oxidative stress, these responsive systems can achieve spatially and temporally controlled drug delivery. However, the clinical translation of these methods is still constrained by multiple challenges such as material biocompatibility, large-scale production, and regulatory preparation. Meanwhile, the continuous integration of nanotechnology and artificial intelligence in the field is bringing new opportunities for the next generation of cardiovascular nanotherapies.

5.1 Challenges

5.1.1 Biosafety and Toxicity

Biological safety is the main obstacle in the clinical translation of nanomedicines, especially in the field of chronic cardiovascular diseases that usually require long-term treatment [340, 341]. Unlike acute diseases, chronic diseases require a comprehensive assessment of the long-term *in vivo* behavior of nanomaterials and their degradation products. Researchers should focus on inorganic nanozymes and imaging contrast agents, and systematically evaluate their long-term biocompatibility and metabolic clearance capabilities. Some inorganic nanomaterials, although showing significant

short-term efficacy, may also have the risks of poor biodegradability or triggering pro-inflammatory responses under continuous exposure [342]. Moreover, there are inherent biological trade-offs in microenvironmental regulation, such as excessive clearance of ROS may interfere with the key signals required for physiological tissue remodeling [343]. Finally, the immunogenicity of nanomaterials can disrupt the consistency of pharmacokinetics and ultimately weaken the sustained therapeutic effect [344].

5.1.2 In Vivo metabolism, targeting and biodistribution

Although the design of nanocarriers is becoming increasingly complex, the actual delivery efficiency of nanoparticles to cardiovascular lesions remains shockingly low. Quantitative biodistribution studies have shown that only a very small proportion of the drug can specifically accumulate in plaques or ischemic myocardium after intravenous injection [345-346]. The poor targeting efficiency is an inevitable consequence of the combined impact of deep physiological and pathological microenvironmental disorders. Nanomedicines must sequentially overcome a series of powerful biological barriers such as macrophage capture, difficulties in endothelial transcellular transport, and poor perfusion of the lesion [347, 348]. Although biomimetic strategies have shown extended circulation half-life in preclinical models, their scalability in clinical translation is still limited. The separation and reconstitution of cell membranes are complex processes, and these factors jointly hinder their compliance with Good Manufacturing Practice (GMP) for large-scale production [349].

5.1.3 Pathological interaction

The pathological microenvironment in CVDs is not static but rather a highly dynamic and biologically complex ecosystem. Its composition and function undergo profound temporal changes, it will successively go through the inflammatory, proliferative and remodeling phases after myocardial infarction [350]. It is crucial that the therapeutic effect highly depends on the timing. If specific interventions are

implemented during the acute phase, it may inhibit the early important immune function. The microenvironment also exhibits substantial interindividual heterogeneity, with multiple plaque phenotypes coexisting within the same patient. The incomplete understanding of the mechanisms of intercellular interactions further exacerbates the complexity of this pathological system. Consequently, the development of next-generation nanotherapeutics capable of spatiotemporal sensing, adaptive payload release, and cell-type-specific engagement remains constrained by inadequate high-resolution characterization of human-relevant microenvironmental states and an incomplete understanding of the causal mechanisms underlying niche-regulated therapeutic responses.

5.1.4 Clinical Translation and Production

Closing the gap between preclinical research and industrial application involves significant engineering and regulatory challenges [351-355]. Many intelligent nanomedicines require complex synthesis processes, which are difficult to achieve cost-effective large-scale production under GMP standards [356]. The existing animal models have limited fidelity in physiology and long-standing transformation bottlenecks that are difficult to overcome [357-359]. Although large animals such as pigs and sheep can simulate human pharmacokinetic characteristics, their application is severely limited by high costs. Before clinical translation, the safety of nanomedicines must be systematically verified in fully characterized large animal models.

5.2 Future Prospects

5.2.1 Artificial Intelligence-based Nanoplatforms

The deep integration of artificial intelligence and machine learning has provided a transformative opportunity to break through the long-standing bottlenecks in the design of nanomaterials [360, 361]. Specifically, algorithms based on AI can efficiently

analyze multi-modal datasets and accurately predict in vivo behaviors, thereby significantly accelerating the screening process for the optimal nanocarriers [362, 363]. Moreover, AI can construct individualized prediction models by integrating multi-dimensional physiological and pathological data, which enable the design of precise and reasonable drug delivery schemes [364, 365].

5.2.2 Synergistic therapy

Significant synergistic therapeutic effects can be produced by combining nanomedicine with complementary advanced therapies. The amalgamation of nanocarriers with external physical stimuli can efficaciously surmount the intrinsic limitations of passive diffusion [366, 367]. At the same time, the nanosystem can also serve as a protective carrier to ensure the integrity of the structure and function of unstable molecules [368]. Notably, nucleic acid therapy has achieved successful transformation in the cardiovascular field, and the approval of inclisiran fully validates the feasibility of targeted nucleic acid delivery [369, 370]. In the future, research on nanosystems will urgently need to conduct large-scale animal experiments to verify their potential for clinical application.

5.2.3 Stimuli-responsive nanoplatforms

The continuous innovation in materials science is of decisive significance for promoting the in-depth development of cardiovascular nanotherapy. Future research should prioritize the creation of new generation biomaterials, enabling to exhibit higher specificity and sensitivity to the microenvironmental characteristics. Among them, the development of intelligent systems based on closed-loop negative feedback regulation holds great promise, as it can regulate drug release in real time according to dynamic physiological signals.

6. Conclusion

The pathological microenvironment plays a crucial role in the progression of cardiovascular diseases, which is not only a major barrier to clinical treatment but also provides an ideal target for precise intervention. Nanomedicine can precisely regulate the complex microenvironment, effectively overcoming the limitations of traditional therapies. Responsive platforms can trigger precise local drug release and significantly reduce systemic toxicity by ingeniously utilizing endogenous stimuli such as tissue acidosis and excessive ROS. This article systematically reviews the latest frontiers of microenvironment-responsive nanotherapies, with a focus on their applications in atherosclerotic plaques and myocardial repair. Although encouraging breakthroughs have been made in recent years, this field still faces severe challenges in terms of long-term biological safety, *in vivo* targeting efficiency, and industrial-scale production. These cutting-edge advancements are crucial for promoting the application of nanotechnology in clinical practice, efficiently reducing the incidence and mortality of cardiovascular diseases.

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Conflict of Interest statement

The authors declare no conflict of interest.

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