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MICRORNA-MEDIATED REGULATION OF MACROPHAGE POLARIZATION IN CARDIOVASCULAR INFLAMMATION AND ATHEROSCLEROTIC DISEASE

Siddarth Raajasekar [1*]

[1]Department of Biotechnology, KIT-KalaignarKarunanidhi Institute of Technology, Coimbatore, India
[*]Corresponding author: Siddarth Raajasekar
Assistant Professor Department: Biotechnology College: KIT-KalaignarKarunanidhi Institute of Technology Email: siddarthraajasekarbiotech@kitcbe.ac.in Orcid: https://orcid.org/0000-0002-1361-0815 Coimbatore Tamil Nadu India

ABSTRACT

Atherosclerosis remains the leading cause of cardiovascular morbidity and mortality worldwide, driven by chronic inflammation and dysregulated lipid metabolism within arterial walls. Macrophages are central orchestrators of atherosclerotic plaque development, with their functional phenotype—ranging from pro-inflammatory M1 to anti-inflammatory M2 states—critically determining plaque stability and disease progression. MicroRNAs (miRNAs), small non-coding RNAs that post-transcriptionally regulate gene expression, have emerged as master regulators of macrophage polarization and function in atherosclerosis. This review synthesizes current evidence on miRNA-mediated control of macrophage phenotype switching, lipid handling, and inflammatory responses in cardiovascular disease. We examine key miRNAs that promote M1 polarization (miR-155, miR-146a, miR-21) and M2 polarization (miR-223, miR-125b, miR-181b), their validated molecular targets, and the signaling pathways they modulate, including NF-κB, TLR4, NLRP3 inflammasome, PI3K/AKT, and PPARγ/LXR axes. Special emphasis is placed on miRNA regulation of cholesterol transport via ABCA1/ABCG1 and foam cell formation. We evaluate the translational potential of miRNAs as circulating biomarkers for cardiovascular risk stratification and as therapeutic targets through antagomirs, mimics, and nanoparticle delivery systems. Despite promising preclinical data, significant challenges remain in delivery specificity, off-target effects, and clinical validation. This comprehensive review highlights the mechanistic complexity of miRNA networks in macrophage biology and identifies critical knowledge gaps that must be addressed to advance miRNA-based cardiovascular therapeutics from bench to bedside.

Keywords: microRNA, macrophage polarization, atherosclerosis, cardiovascular inflammation, cholesterol efflux, therapeutic targeting.

1. INTRODUCTION

Cardiovascular disease (CVD) remains the leading cause of death globally, accounting for approximately 18 million deaths annually, with atherosclerosis as the primary underlying pathology (Zhan et al., 2026). Atherosclerosis is a chronic inflammatory disease characterized by the accumulation of lipids, immune cells, and fibrous elements within arterial walls, leading to plaque formation, vascular stenosis, and acute thrombotic events (Wei et al., 2018). The pathogenesis of atherosclerosis involves complex interactions between endothelial dysfunction, lipid dysregulation, and immune cell activation, with macrophages serving as central orchestrators of disease progression (Zhan et al., 2026).

Macrophages exhibit remarkable phenotypic plasticity, existing along a spectrum from classically activated pro-inflammatory M1 macrophages to alternatively activated anti-inflammatory M2 macrophages (Pasca et al., 2020). In atherosclerotic lesions, the balance between M1 and M2 polarization critically determines plaque stability, with M1-dominant plaques exhibiting increased inflammation, matrix degradation, and vulnerability to rupture, while M2-enriched regions promote tissue repair and plaque stabilization (Rayner et al., 2011). Understanding the molecular mechanisms that govern macrophage polarization is therefore essential for developing targeted therapeutic strategies to prevent plaque progression and reduce cardiovascular events.

MicroRNAs (miRNAs) have emerged as master regulators of macrophage function in atherosclerosis, controlling gene expression networks that determine cellular phenotype, inflammatory responses, and lipid metabolism (Zhan et al., 2026). These small non-coding RNAs, typically 19-25 nucleotides in length, post-transcriptionally regulate gene expression by binding to complementary sequences in target messenger RNAs (mRNAs), leading to translational repression or mRNA degradation (Wei et al., 2018). Individual miRNAs can regulate hundreds of target genes, while single genes may be controlled by multiple miRNAs, creating complex regulatory networks that fine-tune cellular responses to environmental stimuli (Euler et al., 2025).

Recent advances in high-throughput sequencing and functional genomics have identified numerous miRNAs that regulate macrophage polarization and atherosclerotic disease progression. Key miRNAs such as miR-155, miR-146a, miR-33, and miR-223 have been extensively characterized for their roles in modulating inflammatory signaling pathways, cholesterol transport, and foam cell formation (Zhan et al., 2026; Ouimet et al., 2015; Rayner et al., 2011). Moreover, circulating miRNAs have shown promise as non-invasive biomarkers for cardiovascular risk assessment and disease monitoring (Zaidi et al., 2025). Therapeutic modulation of miRNA activity through antagomirs, mimics, and advanced delivery systems has demonstrated efficacy in preclinical models, raising the possibility of miRNA-based interventions for atherosclerosis treatment (Wan et al., 2026; Li et al., 2025).

This comprehensive review synthesizes current knowledge on miRNA-mediated regulation of macrophage polarization in cardiovascular inflammation and atherosclerotic disease. We examine the molecular mechanisms by which specific miRNAs control M1 and M2 phenotype switching, their regulation of cholesterol metabolism and foam cell formation, and their roles in plaque development and stability. We critically evaluate the translational potential of miRNAs as biomarkers and therapeutic targets, while identifying key knowledge gaps and future research directions needed to advance this field toward clinical application.

2. MACROPHAGE POLARIZATION IN CARDIOVASCULAR DISEASE

2.1 Monocyte Recruitment and Differentiation

The initiation of atherosclerosis begins with endothelial dysfunction triggered by cardiovascular risk factors including hyperlipidemia, hypertension, diabetes, and smoking (Zhan et al., 2026). Dysfunctional endothelium exhibits increased permeability to low-density lipoprotein (LDL) particles, which become trapped in the subendothelial space where they undergo oxidative modification to form oxidized LDL (oxLDL) (Wu et al., 2024). OxLDL activates endothelial cells to express adhesion molecules including vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), and E-selectin, which mediate the capture and firm adhesion of circulating monocytes (Zhan et al., 2026).

Chemokine gradients, particularly monocyte chemoattractant protein-1 (MCP-1/CCL2) and its receptor CCR2, direct monocyte transmigration into the arterial intima (Mallén et al., 2025). Once in the subendothelial space, monocytes differentiate into macrophages under the influence of macrophage colony-stimulating factor (M-CSF) and local microenvironmental cues (Zhan et al., 2026). The phenotype adopted by these newly differentiated macrophages depends on the balance of polarizing signals present in the lesion microenvironment, with interferon-gamma (IFN-γ) and lipopolysaccharide (LPS) promoting M1 polarization, while interleukin-4 (IL-4) and interleukin-13 (IL-13) drive M2 differentiation (Pasca et al., 2020).

Recent evidence indicates that miRNAs regulate multiple steps in monocyte recruitment and differentiation. For example, miR-125b-5p modulates monocyte trafficking through regulation of the CCR7 receptor, with in vivo inhibition of miR-125b-5p reducing atherosclerosis in experimental models (Mallén et al., 2025). These findings highlight the importance of miRNA-mediated control of early atherogenic processes that precede macrophage polarization.

2.2 M1 Macrophages: Pro-inflammatory Phenotype

M1 macrophages, also termed classically activated macrophages, are induced by pro-inflammatory stimuli including IFN-γ, LPS, and tumor necrosis factor-alpha (TNF-α) (Pasca et al., 2020). These cells are characterized by high expression of inducible nitric oxide synthase (iNOS), production of reactive oxygen and nitrogen species, and secretion of pro-inflammatory cytokines including TNF-α, interleukin-1 beta (IL-1β), interleukin-6 (IL-6), and interleukin-12 (IL-12) (Zhan et al., 2026). M1 macrophages exhibit enhanced microbicidal and tumoricidal activity, reflecting their role in host defense against pathogens and malignant cells (Pasca et al., 2020).

In atherosclerotic lesions, M1 macrophages contribute to plaque progression and instability through multiple mechanisms. They produce matrix metalloproteinases (MMPs) that degrade the fibrous cap, increasing vulnerability to rupture (Zhan et al., 2026). M1-derived reactive oxygen species promote further LDL oxidation, creating a positive feedback loop that amplifies inflammation (Wu et al., 2024). Additionally, M1 macrophages activate the NLRP3 inflammasome, leading to caspase-1-dependent processing and secretion of mature IL-1β and IL-18, which further propagate inflammatory responses (Zhan et al., 2026).

The transcriptional program of M1 macrophages is orchestrated by key transcription factors including nuclear factor-kappa B (NF-κB), signal transducer and activator of transcription 1 (STAT1), and interferon regulatory factors (IRFs) (Zhan et al., 2026). Activation of Toll-like receptor 4 (TLR4) by oxLDL or damage-associated molecular patterns

(DAMPs) triggers downstream signaling cascades involving myeloid differentiation primary response 88 (MyD88), interleukin-1 receptor-associated kinase (IRAK), and TNF receptor-associated factor 6 (TRAF6), culminating in NF-κB nuclear translocation and pro-inflammatory gene transcription (Yang et al., 2023). MicroRNAs such as miR-155 and miR-21 amplify M1 polarization by targeting negative regulators of these inflammatory pathways, as discussed in detail in Section 4 (Nazari-Jahantigh et al., 2012; Wu et al., 2024).

2.3 M2 Macrophages: Anti-inflammatory and Reparative Phenotype

M2 macrophages, or alternatively activated macrophages, represent a heterogeneous population induced by IL-4, IL-13, IL-10, transforming growth factor-beta (TGF-β), and glucocorticoids (Pasca et al., 2020). M2 macrophages are characterized by high expression of arginase-1 (Arg1), which metabolizes arginine to ornithine and polyamines that support tissue repair, in contrast to M1 macrophages that use arginine for nitric oxide production via iNOS (Rayner et al., 2011). Additional M2 markers include mannose receptor (CD206), chitinase-like proteins (Ym1/Ym2), resistin-like molecule alpha (FIZZ1/RELM-α), and scavenger receptor CD163 (Zhan et al., 2026).

M2 macrophages produce anti-inflammatory cytokines including IL-10 and TGF-β, which suppress pro-inflammatory responses and promote tissue remodeling (Rayner et al., 2011). They exhibit enhanced phagocytic capacity for apoptotic cells (efferocytosis), a critical process for resolving inflammation and preventing necrotic core formation in atherosclerotic plaques (Bouchareychas et al., 2020). M2 macrophages also promote angiogenesis, extracellular matrix deposition, and wound healing, contributing to plaque stabilization (Zhan et al., 2026).

The M2 phenotype is regulated by transcription factors including STAT6, peroxisome proliferator-activated receptor gamma (PPARγ), and Krüppel-like factor 4 (KLF4) (Zhan et al., 2026). PPARγ activation promotes expression of genes involved in lipid metabolism and cholesterol efflux, including ATP-binding cassette transporters ABCA1 and ABCG1, which facilitate reverse cholesterol transport and reduce foam cell formation (Zhou et al., 2023). MicroRNAs such as miR-223, miR-125b, and miR-126 promote M2 polarization and enhance cholesterol efflux, contributing to atheroprotective effects (Rayner et al., 2011; Mallén et al., 2025; Zhan et al., 2026).

2.4 Foam Cell Formation and Lipid Accumulation

Foam cells, lipid-laden macrophages that constitute the hallmark of atherosclerotic lesions, form when macrophage cholesterol uptake exceeds cholesterol efflux capacity (Zhan et al., 2026). Macrophages internalize modified lipoproteins, particularly oxLDL and acetylated LDL, through scavenger receptors including scavenger receptor class A (SR-A), CD36, and lectin-like oxidized LDL receptor-1 (LOX-1) (Zhan et al., 2026). Unlike the LDL receptor, which is downregulated by intracellular cholesterol accumulation, scavenger receptors are not subject to feedback inhibition, allowing unregulated lipid uptake that drives foam cell formation (Wei et al., 2018).

Cholesterol efflux from macrophages occurs primarily through ABCA1 and ABCG1 transporters, which mediate cholesterol transfer to lipid-poor apolipoprotein A-I (apoA-I) and mature high-density lipoprotein (HDL) particles, respectively (Rayner et al., 2011). This process, termed reverse cholesterol transport (RCT), represents the primary mechanism for removing excess cholesterol from peripheral tissues, including atherosclerotic plaques, for delivery to the liver and excretion (Ouimet et al., 2015). The balance between cholesterol uptake and efflux determines whether macrophages accumulate lipid and transform into foam cells or maintain cholesterol homeostasis (Zhan et al., 2026).

MicroRNAs play critical roles in regulating both arms of macrophage cholesterol metabolism. miR-33, encoded within introns of sterol regulatory element-binding protein (SREBP) genes, directly targets ABCA1 and ABCG1, suppressing cholesterol efflux and promoting foam cell formation (Ouimet et al., 2015; Rayner et al., 2011). Conversely, miR-223 promotes cholesterol efflux by targeting the transcription factor Sp3, which represses ABCA1 expression (Circulation Research, 2022). The therapeutic potential of modulating these miRNAs to enhance cholesterol efflux and reduce foam cell burden is discussed in Sections 6 and 9.

2.5 Plaque Progression and Instability

Atherosclerotic plaque progression involves the gradual accumulation of lipids, inflammatory cells, smooth muscle cells, and extracellular matrix within the arterial wall, leading to luminal narrowing and impaired blood flow (Zhan et al., 2026). However, the clinical manifestations of atherosclerosis—myocardial infarction, stroke, and peripheral arterial disease—result primarily from acute thrombotic occlusion following plaque rupture or erosion rather than gradual stenosis (Wei et al., 2018). Vulnerable plaques prone to rupture are characterized by a large necrotic core rich in foam cells and cellular debris, a thin fibrous cap with reduced collagen content, and abundant inflammatory cells, particularly M1 macrophages (Zhan et al., 2026).

M1 macrophages destabilize plaques through multiple mechanisms. They secrete MMPs, particularly MMP-2, MMP-9, and MMP-12, which degrade collagen and elastin in the fibrous cap (Zhan et al., 2026). M1-derived pro-inflammatory cytokines inhibit smooth muscle cell proliferation and collagen synthesis, further weakening the cap

(Pasca et al., 2020). Additionally, M1 macrophages undergo apoptosis and necrosis in the lipid-rich core, contributing to necrotic core expansion and release of pro-thrombotic tissue factor (Wei et al., 2018). Defective efferocytosis—the clearance of apoptotic cells—exacerbates necrotic core formation and inflammation (Bouchareychas et al., 2020).

In contrast, M2 macrophages promote plaque stability by secreting anti-inflammatory cytokines, enhancing efferocytosis, and supporting fibrous cap integrity through production of extracellular matrix components (Rayner et al., 2011). Therapeutic strategies that shift the macrophage phenotype from M1 to M2, including miRNA-based interventions, hold promise for stabilizing vulnerable plaques and preventing acute cardiovascular events (Wan et al., 2026; Li et al., 2025). The dynamic balance between M1 and M2 macrophages, regulated in part by miRNA networks, thus represents a critical determinant of plaque fate and clinical outcomes in atherosclerotic disease (Zhan et al., 2026) (figure 1).

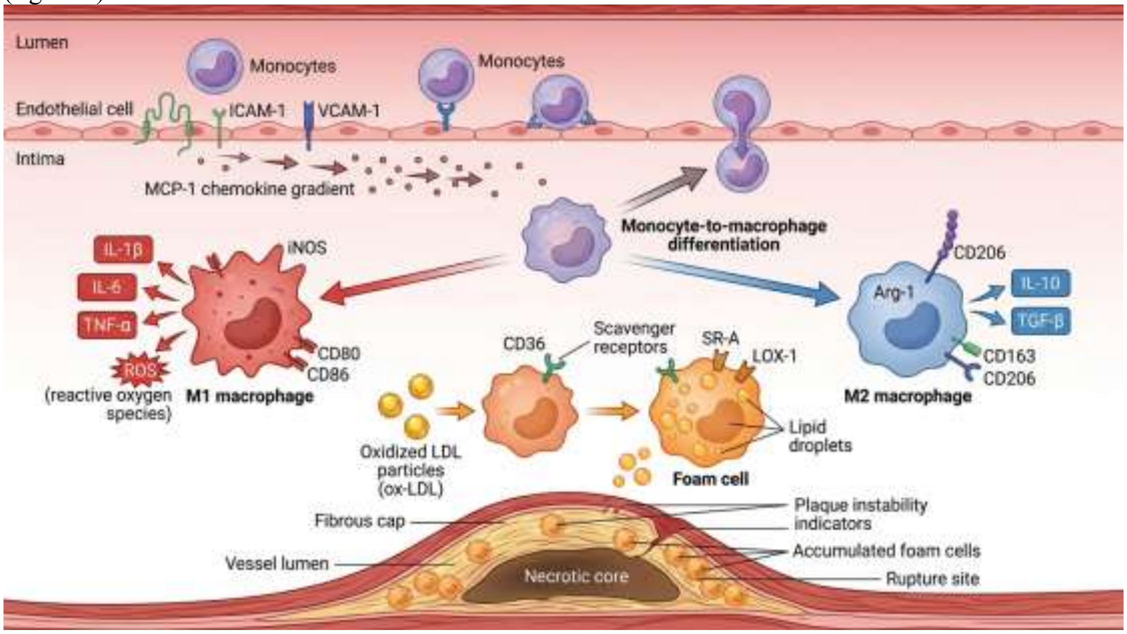

Figure 1. Macrophage polarization in atherosclerosis. Monocyte recruitment, M1/M2 polarization, inflammatory cytokine production, foam-cell formation, and plaque progression.

3. BIOGENESIS AND FUNCTION OF MICRORNAS

MicroRNAs are small non-coding RNA molecules, typically 19-25 nucleotides in length, that regulate gene expression post-transcriptionally by binding to complementary sequences in the 3’ untranslated region (3’UTR) of target mRNAs (Wei et al., 2018). Since their discovery in Caenorhabditis elegans in 1993 and subsequent identification in mammals, over 2,600 mature human miRNAs have been catalogued, collectively regulating an estimated 60% of protein-coding genes (Euler et al., 2025). MicroRNAs play fundamental roles in development, differentiation, proliferation, apoptosis, and metabolism, with dysregulation implicated in diverse pathological conditions including cancer, metabolic disorders, and cardiovascular disease (Zaidi et al., 2025).

The biogenesis of miRNAs involves multiple processing steps coordinated between the nucleus and cytoplasm (Wei et al., 2018). MicroRNA genes are transcribed by RNA polymerase II to generate long primary transcripts (pri-miRNAs) containing hairpin structures. In the nucleus, the microprocessor complex, consisting of the RNase III enzyme Drosha and its cofactor DGCR8, cleaves pri-miRNAs to produce approximately 70-nucleotide precursor miRNAs (pre-miRNAs) with characteristic stem-loop structures (Euler et al., 2025). Pre-miRNAs are exported to the cytoplasm by exportin-5 in a RAN-GTP-dependent manner, where they undergo further processing by the RNase III enzyme Dicer, which removes the terminal loop to generate a miRNA duplex (Wei et al., 2018).

One strand of the miRNA duplex, termed the guide strand or mature miRNA, is preferentially loaded into the RNA-induced silencing complex (RISC), while the complementary passenger strand is typically degraded (Euler et al., 2025). The core component of RISC is an Argonaute (AGO) protein, with AGO2 being the primary catalytic member in mammals. The miRNA guides RISC to target mRNAs through base-pairing interactions, with the “seed sequence” (nucleotides 2-8 from the 5’ end of the miRNA) playing a critical role in target recognition (Wei et al., 2018). Perfect or near-perfect complementarity between the miRNA and target mRNA, common in plants but rare in animals, leads to AGO2-mediated endonucleolytic cleavage of the target. More commonly in mammals, partial complementarity results in translational repression and/or mRNA destabilization through deadenylation and decay (Euler et al., 2025). The regulatory impact of individual miRNAs is amplified by their ability to target multiple mRNAs, often within the same biological pathway or functional network (Zhan et al., 2026). Conversely, individual mRNAs may contain binding sites for multiple miRNAs, allowing combinatorial regulation and fine-tuning of gene expression (Wei et al., 2018). This many-to-many relationship creates complex regulatory networks that integrate diverse cellular signals and coordinate cellular responses. In macrophages, miRNA networks regulate key processes including polarization, inflammatory cytokine production, phagocytosis, and lipid metabolism, positioning them as master regulators of macrophage function in atherosclerosis (Zhan et al., 2026).

MicroRNAs exhibit cell-type-specific and context-dependent expression patterns, with their levels dynamically regulated by developmental cues, environmental stimuli, and pathological conditions (Euler et al., 2025). In atherosclerosis, specific miRNAs are differentially expressed in lesional macrophages compared to circulating monocytes or tissue-resident macrophages in healthy vessels (Fitzsimons et al., 2020). Moreover, miRNAs can be secreted from cells in extracellular vesicles, including exosomes and microvesicles, or bound to AGO proteins or lipoproteins, allowing intercellular communication and systemic regulation (Bouchareychas et al., 2020; Zhou et al., 2023). Circulating miRNAs have emerged as promising biomarkers for cardiovascular disease, reflecting pathological processes in the vessel wall and correlating with disease severity and prognosis (Zaidi et al., 2025).

The therapeutic potential of targeting miRNAs in disease has driven development of miRNA-based interventions, including miRNA mimics to restore deficient miRNAs and antagomirs or antisense oligonucleotides to inhibit pathogenic miRNAs (Wan et al., 2026; Li et al., 2025). Chemical modifications, including 2’-O-methyl, 2’-O-methoxyethyl, and locked nucleic acid (LNA) modifications, enhance stability, binding affinity, and resistance to nuclease degradation (Euler et al., 2025). Advanced delivery systems, including lipid nanoparticles, polymeric nanoparticles, and exosomes, enable targeted delivery to specific cell types and tissues, improving efficacy while minimizing off-target effects (Wan et al., 2026; Zhou et al., 2023). These technological advances have positioned miRNA therapeutics at the forefront of precision medicine approaches for cardiovascular disease.

4. MICRORNA REGULATION OF M1 POLARIZATION

4.1 miR-155

MicroRNA-155 is one of the most extensively studied pro-inflammatory miRNAs in atherosclerosis, with robust evidence demonstrating its role in promoting M1 macrophage polarization and exacerbating vascular inflammation (Nazari-Jahantigh et al., 2012; Pasca et al., 2020). miR-155 is encoded by the B-cell integration cluster (BIC) gene and is rapidly upregulated in macrophages following stimulation with LPS, IFN-γ, TNF-α, and oxLDL (Pasca et al., 2020). In atherosclerotic lesions, miR-155 expression is elevated in macrophage-rich regions, correlating with plaque inflammation and instability (Fitzsimons et al., 2020).

The pro-inflammatory effects of miR-155 are mediated through targeting of multiple negative regulators of inflammatory signaling pathways. A key validated target is B-cell lymphoma 6 (Bcl6), a transcriptional repressor that suppresses NF-κB-dependent inflammatory gene expression (Nazari-Jahantigh et al., 2012). By repressing Bcl6, miR-155 relieves inhibition of NF-κB signaling, resulting in enhanced production of pro-inflammatory cytokines including TNF-α, IL-6, and IL-1β (Nazari-Jahantigh et al., 2012). Additional targets of miR-155 include suppressor of cytokine signaling 1 (SOCS1), which negatively regulates JAK/STAT signaling, and inositol polyphosphate-5-phosphatase D (SHIP1), which modulates PI3K/AKT pathway activity (Pasca et al., 2020). Through these mechanisms, miR-155 amplifies inflammatory responses and promotes M1 polarization (Zhan et al., 2026).

Genetic studies in mouse models have provided compelling evidence for the pro-atherogenic role of miR-155. Deficiency of miR-155 in apolipoprotein E-knockout (ApoE-/-) mice results in decreased macrophage inflammation, reduced atherosclerotic lesion size, and improved plaque stability (Nazari-Jahantigh et al., 2012). Conversely, overexpression of miR-155 exacerbates atherosclerosis and increases plaque vulnerability (Nazari-Jahantigh et al., 2012). Mechanistically, miR-155-deficient macrophages exhibit reduced expression of M1 markers (iNOS, TNF-α, IL-6) and enhanced expression of M2 markers (Arg1, IL-10), indicating a shift toward an anti-inflammatory phenotype (Bruen et al., 2019).

Interestingly, the role of miR-155 in atherosclerosis may be context-dependent and stage-specific. While miR-155 promotes inflammation during plaque progression, some evidence suggests it may contribute to inflammation resolution during plaque regression (Bruen et al., 2019). During regression induced by lipid-lowering therapy, miR-155 expression decreases in lesional macrophages, correlating with reduced inflammation and increased M2 polarization (Fitzsimons et al., 2020). These findings suggest that the balance of miR-155 expression must be carefully considered when developing therapeutic strategies targeting this miRNA (Bruen et al., 2019).

4.2 miR-146a

MicroRNA-146a exhibits complex and context-dependent roles in macrophage polarization and atherosclerosis, functioning primarily as a negative feedback regulator of inflammatory signaling (Zhan et al., 2026). miR-146a is induced by NF-κB activation in response to TLR ligands and pro-inflammatory cytokines, representing an endogenous mechanism to limit excessive inflammation (Pasca et al., 2020). In macrophages, miR-146a targets key components of TLR and NF-κB signaling pathways, including IRAK1, TRAF6, and IRAK2, thereby attenuating inflammatory responses (Zhan et al., 2026).

Despite its anti-inflammatory function in dampening TLR signaling, the net effect of miR-146a on atherosclerosis appears complex and may depend on disease stage and cellular context. Some studies report that miR-146a deficiency exacerbates atherosclerosis in mouse models, consistent with a protective role through inflammation suppression (Zhan et al., 2026). However, other evidence suggests that miR-146a may promote certain aspects of M1 polarization under specific conditions, highlighting the need for careful interpretation of its functional roles (Pasca et al., 2020).

The therapeutic potential of miR-146a has been explored through delivery of miR-146a mimics to reprogram macrophage phenotype and reduce plaque inflammation. A recent study developed a miRNA and reactive oxygen species (ROS)-scavenger co-loaded nanogel that delivered miR-146a-5p to atherosclerotic lesions, achieving macrophage reprogramming toward an anti-inflammatory phenotype and significant reduction in plaque inflammation in preclinical models (Wan et al., 2026). This nanogel system combined miR-146a delivery with ROS scavenging to address both inflammatory signaling and oxidative stress, two interconnected drivers of atherosclerosis (Wan et al., 2026). The nanogel was also MRI-visible, enabling non-invasive monitoring of therapeutic delivery and efficacy (Wan et al., 2026).

These findings position miR-146a as a promising therapeutic target for atherosclerosis, with the caveat that delivery strategies must achieve sufficient specificity for lesional macrophages to avoid off-target effects in other cell types where miR-146a may have different functional roles (Wan et al., 2026). The development of advanced delivery systems, such as the ROS-scavenger nanogel, represents an important step toward translating miR-146a-based therapies into clinical applications (Wan et al., 2026).

4.3 miR-21

MicroRNA-21 is one of the most abundantly expressed miRNAs in cardiovascular tissues and has been implicated in diverse pathological processes including fibrosis, hypertrophy, and inflammation (Wei et al., 2018). In the context of atherosclerosis, miR-21 promotes M1 macrophage polarization through a complex intercellular signaling mechanism involving endothelial cells and macrophages (Wu et al., 2024). OxLDL stimulation of endothelial cells induces miR-21-5p expression, which targets S-phase kinase-associated protein 2 (SKP2), a component of the SCF ubiquitin ligase complex (Wu et al., 2024).

Downregulation of SKP2 by miR-21-5p leads to altered ubiquitination and stabilization of E1A-binding protein p300 (EP300), a histone acetyltransferase that regulates chromatin structure and gene transcription (Wu et al., 2024). Stabilized EP300 promotes acetylation and nuclear translocation of high mobility group box 1 (HMGB1), a damage-associated molecular pattern (DAMP) that is subsequently secreted from endothelial cells (Wu et al., 2024). Extracellular HMGB1 acts as a pro-inflammatory signal that binds to receptors on macrophages, including TLR4 and receptor for advanced glycation end products (RAGE), triggering inflammatory signaling cascades that promote M1 polarization (Wu et al., 2024).

This miR-21-5p/SKP2/EP300/HMGB1 axis represents a novel mechanism of endothelial-macrophage crosstalk in atherosclerosis, wherein endothelial miR-21 indirectly promotes macrophage M1 polarization through paracrine HMGB1 signaling (Wu et al., 2024). The identification of this pathway highlights the importance of considering intercellular communication networks when studying miRNA function in complex tissues such as atherosclerotic plaques (Wu et al., 2024). Therapeutic strategies targeting miR-21 may need to account for its effects in multiple cell types, including both endothelial cells and macrophages, to achieve optimal efficacy (Wu et al., 2024) (figure 2).

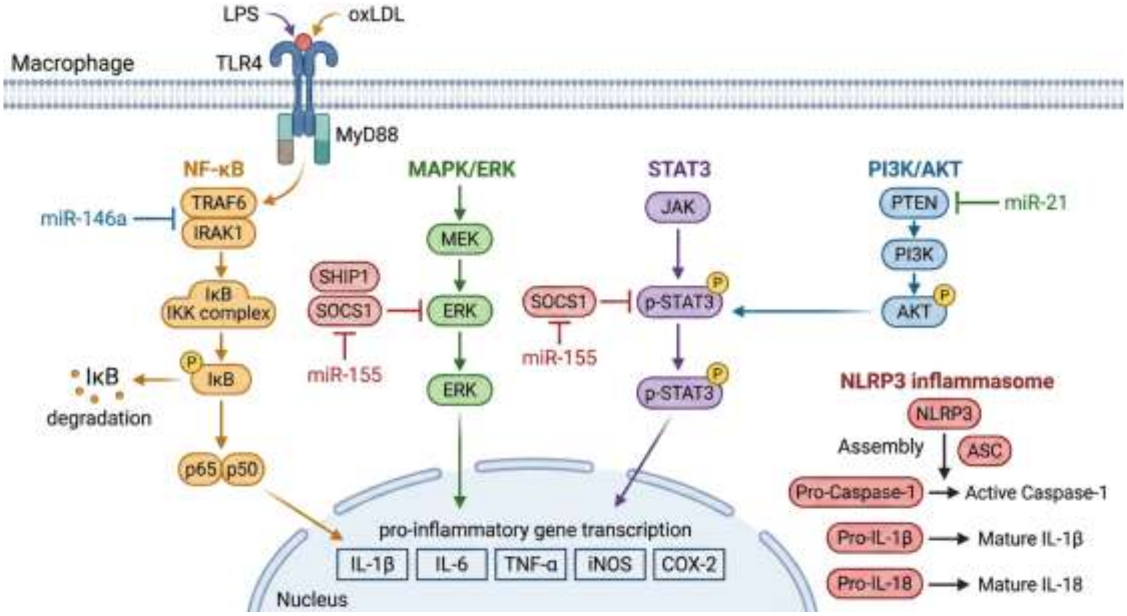

Figure 2. MicroRNA regulation of M1 macrophage polarization through NF-κB, STAT3, TLR4, and NLRP3 signaling pathways.

5. MICRORNA REGULATION OF M2 POLARIZATION

5.1 miR-223

MicroRNA-223 is a myeloid-enriched miRNA that plays a critical atheroprotective role by promoting anti-inflammatory macrophage phenotype and enhancing cholesterol efflux (Circulation Research, 2022). miR-223 is highly expressed in mature macrophages and is dynamically regulated during monocyte-to-macrophage differentiation (Circulation Research, 2022). In atherosclerotic lesions, miR-223 expression correlates inversely with plaque inflammation and lipid content, suggesting a protective function (Circulation Research, 2022).

The atheroprotective effects of miR-223 are mediated through targeting of the transcription factor specificity protein 3 (Sp3), which represses expression of genes involved in cholesterol efflux and anti-inflammatory responses (Circulation Research, 2022). By suppressing Sp3, miR-223 relieves transcriptional repression of ABCA1, the primary cholesterol efflux transporter, thereby enhancing cholesterol efflux to apoA-I and reducing foam cell formation (Circulation Research, 2022). Additionally, miR-223 regulates translation of genes involved in cholesterol biosynthesis and NF-κB signaling pathways, exerting broad control over macrophage lipid metabolism and inflammatory responses (Circulation Research, 2022).

Genetic studies in mice have demonstrated the functional importance of miR-223 in atherosclerosis. Mice receiving miR-223-deficient bone marrow exhibit increased atherosclerotic plaque size, elevated lipid content, and enhanced inflammation compared to controls (Circulation Research, 2022). Mechanistically, loss of miR-223 in macrophages decreases ABCA1 expression and cholesterol efflux to apoA-I, while enhancing pro-inflammatory gene expression (Circulation Research, 2022). Conversely, overexpression of miR-223 promotes cholesterol efflux and anti-inflammatory macrophage phenotype, reducing atherosclerosis in experimental models (Circulation Research, 2022).

The dual function of miR-223 in regulating both cholesterol metabolism and inflammation positions it as an attractive therapeutic target for atherosclerosis. Strategies to enhance miR-223 activity in lesional macrophages, through delivery of miR-223 mimics or activation of endogenous miR-223 expression, may simultaneously reduce foam cell formation and suppress inflammation, addressing two key pathogenic mechanisms in atherosclerosis (Circulation Research, 2022). However, the myeloid-enriched expression pattern of miR-223 suggests that its functions may be cell-type-specific, necessitating careful consideration of delivery strategies to target macrophages while avoiding effects in other hematopoietic lineages (Circulation Research, 2022).

5.2 miR-125b

MicroRNA-125b regulates multiple aspects of atherosclerosis pathogenesis, including monocyte trafficking, endothelial inflammation, and macrophage polarization (Mallén et al., 2025). In vivo inhibition of miR-125b-5p reduces atherosclerosis by modulating CCR7-dependent monocyte trafficking, demonstrating a pro-atherogenic role for this miRNA in regulating immune cell recruitment to lesions (Mallén et al., 2025). The CCR7 receptor mediates chemotaxis of monocytes and dendritic cells in response to CCL19 and CCL21 chemokines, and its regulation by miR-125b influences the magnitude of monocyte infiltration into atherosclerotic plaques (Mallén et al., 2025).

In endothelial cells, miR-125b-5p has been shown to ameliorate oxLDL-induced inflammation by negatively regulating TLR4/NF-κB signaling pathway components, reducing endothelial production of pro-inflammatory mediators that promote M1 macrophage polarization (Mallén et al., 2025).

The context-dependent and cell-type-specific functions of miR-125b in atherosclerosis highlight the complexity of miRNA networks in vascular disease and the importance of considering cellular context when interpreting functional studies and designing therapeutic interventions (Mallén et al., 2025). The net effect of miR-125b modulation on atherosclerosis likely depends on the balance of its effects across multiple cell types and disease stages (Mallén et al., 2025).

5.3 miR-181b

MicroRNA-181b exerts anti-inflammatory effects in vascular cells by modulating NLRP3 inflammasome activation and inflammatory signaling pathways (An et al., 2017). The NLRP3 inflammasome is a multiprotein complex that senses cellular stress signals, including cholesterol crystals, reactive oxygen species, and lysosomal damage, leading to caspase-1 activation and processing of pro-IL-1β and pro-IL-18 into their mature, secreted forms (Zhan et al., 2026). Excessive inflammasome activation contributes to chronic inflammation in atherosclerotic plaques and promotes plaque instability (Zhan et al., 2026).

miR-181b-5p suppresses pro-inflammatory signaling by targeting key pathway components, thereby reducing IL-1β production and limiting inflammatory cell death (An et al., 2017). Pyroptosis is a form of inflammatory cell death characterized by plasma membrane rupture and release of intracellular contents, including pro-inflammatory cytokines and DAMPs, which amplify inflammation in the local microenvironment (Zhan et al., 2026). By modulating these pathways, miR-181b-5p reduces the inflammatory burden in atherosclerotic lesions and may promote plaque stability (An et al., 2017).

In addition to its effects on inflammasome signaling, miR-181b has been reported to antagonize atherosclerotic plaque vulnerability through modulation of macrophage polarization by directly targeting Notch1 (An et al., 2017). Notch signaling regulates macrophage differentiation and polarization, with Notch1 activation promoting M1 phenotype and Notch2 activation favoring M2 phenotype (An et al., 2017). By targeting Notch1, miR-181b shifts the balance toward M2 polarization, reducing inflammation and promoting tissue repair (An et al., 2017). These findings position miR-181b as a multifunctional regulator of macrophage phenotype and inflammatory signaling, with therapeutic potential for stabilizing vulnerable plaques (An et al., 2017) (figure 3).

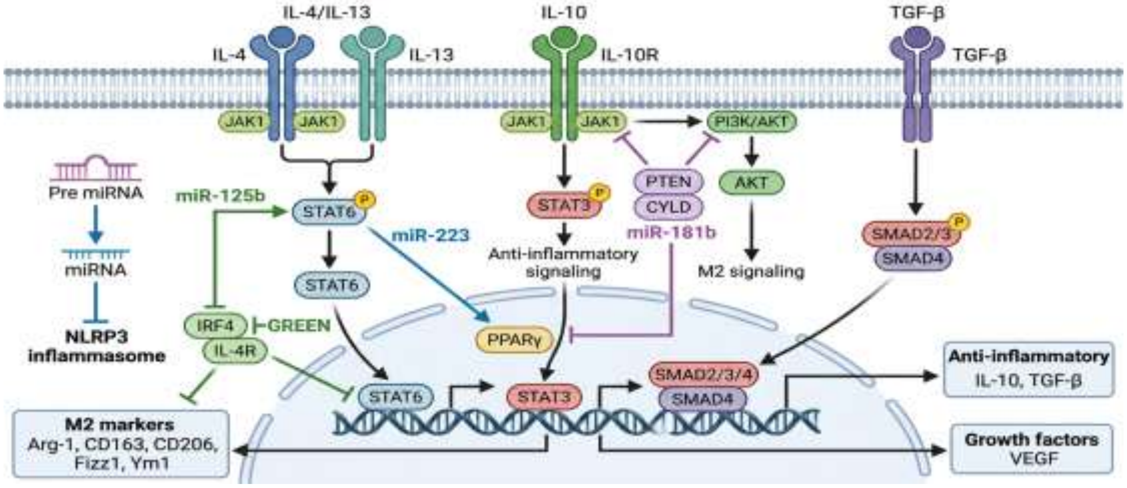

Figure 3. MicroRNA regulation of M2 macrophage polarization involving miR-223, miR-125b, miR-181b, PPARγ, IL-10, and TGF-β signaling.

6. MICRORNAS AND FOAM-CELL BIOLOGY

6.1 Cholesterol Uptake Mechanisms

Foam cell formation represents a critical early event in atherosclerosis, driven by macrophage uptake of modified lipoproteins that exceeds the capacity for cholesterol efflux (Zhan et al., 2026). Macrophages internalize oxLDL and other modified lipoproteins through scavenger receptors, including SR-A (also known as MSR1), CD36, and LOX-1 (Zhan et al., 2026). Unlike the classical LDL receptor (LDLR), which is subject to negative feedback regulation by intracellular cholesterol levels, scavenger receptors are not downregulated by cholesterol accumulation, allowing uncontrolled lipid uptake that drives foam cell transformation (Wei et al., 2018).

CD36 is a class B scavenger receptor that binds oxLDL with high affinity and mediates its internalization through clathrin-dependent and -independent endocytic pathways (Zhan et al., 2026). SR-A recognizes a broad range of modified lipoproteins and also participates in uptake of apoptotic cells and bacteria, reflecting its role in innate immunity (Zhan et al., 2026). LOX-1, the primary oxLDL receptor in endothelial cells, is also expressed in macrophages and contributes to foam cell formation (Wei et al., 2018). Activation of these scavenger receptors by oxLDL triggers intracellular signaling cascades that promote inflammatory responses, creating a positive feedback loop linking lipid accumulation and inflammation (Zhan et al., 2026).

While miRNAs are well-established regulators of cholesterol efflux pathways (discussed in Section 6.2), direct evidence for miRNA regulation of scavenger receptor expression in macrophages remains limited in the current literature (Zhan et al., 2026). Most studies have focused on miRNA control of ABCA1, ABCG1, and related efflux mechanisms rather than uptake receptors (Ouimet et al., 2015; Rayner et al., 2011). This represents an important knowledge gap, as therapeutic strategies that simultaneously reduce cholesterol uptake and enhance efflux may be more effective than targeting efflux alone (Zhan et al., 2026). Future research should investigate whether specific miRNAs regulate scavenger receptor expression and whether modulation of these miRNAs can reduce foam cell formation by limiting lipid uptake (Zhan et al., 2026).

6.2 Reverse Cholesterol Transport

Reverse cholesterol transport (RCT) is the process by which excess cholesterol is removed from peripheral tissues, including atherosclerotic plaques, and delivered to the liver for excretion in bile (Rayner et al., 2011). RCT represents the primary mechanism for reducing foam cell cholesterol burden and is a critical determinant of atherosclerosis progression (Ouimet et al., 2015). The initial and rate-limiting step of RCT is cholesterol efflux from macrophages to extracellular acceptors, primarily lipid-poor apoA-I and mature HDL particles (Rayner et al., 2011).

Macrophage cholesterol efflux occurs through multiple pathways. ABCA1 mediates cholesterol and phospholipid efflux to lipid-poor apoA-I, generating nascent HDL particles (Rayner et al., 2011). ABCG1 facilitates cholesterol efflux to mature HDL particles (Ouimet et al., 2015). Additionally, passive diffusion and SR-BI (scavenger receptor class B type I)-mediated bidirectional cholesterol flux contribute to cholesterol efflux, particularly to mature HDL (Rayner et al., 2011). The relative contribution of these pathways depends on the availability of extracellular acceptors and the expression levels of transporters (Ouimet et al., 2015).

Following efflux from macrophages, cholesterol is transported in HDL particles to the liver, where it is taken up by hepatic SR-BI and secreted into bile, either directly or after conversion to bile acids (Rayner et al., 2011). Biliary cholesterol is then excreted in feces, completing the RCT pathway (Rayner et al., 2011). Epidemiological studies have consistently demonstrated an inverse relationship between HDL cholesterol levels and cardiovascular disease risk, attributed in part to the role of HDL in RCT (Ouimet et al., 2015). However, recent clinical trials of HDL-raising therapies have yielded disappointing results, suggesting that HDL function (particularly cholesterol efflux capacity) may be more important than HDL quantity for cardiovascular protection (Rayner et al., 2011).

MicroRNAs play critical roles in regulating RCT at multiple levels. miR-33, encoded within introns of SREBP genes, directly targets ABCA1 and ABCG1, suppressing cholesterol efflux and RCT (Ouimet et al., 2015; Rayner et al., 2011). miR-223 promotes cholesterol efflux by targeting Sp3, a transcriptional repressor of ABCA1 (Circulation Research, 2022). These findings have motivated development of miRNA-based therapeutic strategies to enhance RCT and reduce atherosclerosis, as discussed in Section 9 (Rayner et al., 2011; Ouimet et al., 2015).

6.3 ABCA1 and ABCG1 Regulation

ABCA1 and ABCG1 are ATP-binding cassette transporters that play central roles in macrophage cholesterol efflux and RCT (Rayner et al., 2011). ABCA1 mediates the efflux of cholesterol and phospholipids to lipid-poor apoA-I, the primary protein component of HDL (Rayner et al., 2011). This process generates nascent HDL particles that are subsequently matured through acquisition of additional lipids and apolipoproteins (Ouimet et al., 2015). ABCG1 facilitates cholesterol efflux to mature HDL particles, complementing the function of ABCA1 (Ouimet et al., 2015). Together, ABCA1 and ABCG1 account for the majority of cholesterol efflux from macrophages to HDL acceptors (Rayner et al., 2011).

Expression of ABCA1 and ABCG1 is transcriptionally regulated by the nuclear receptors liver X receptor alpha (LXRα) and PPARγ, which sense intracellular cholesterol levels and activate compensatory efflux mechanisms (Ouimet et al., 2015). When intracellular cholesterol accumulates, oxysterols (oxidized cholesterol derivatives) activate LXRα, which heterodimerizes with retinoid X receptor (RXR) and binds to LXR response elements in the promoters of ABCA1 and ABCG1, inducing their transcription (Rayner et al., 2011). PPARγ activation by fatty acids and synthetic agonists also upregulates ABCA1 and ABCG1 expression, promoting cholesterol efflux and M2 macrophage polarization (Zhou et al., 2023).

miR-33 is a key post-transcriptional regulator of ABCA1 and ABCG1 expression (Ouimet et al., 2015). miR-33 is encoded within introns of SREBP2 (miR-33a) and SREBP1 (miR-33b in humans), transcription factors that activate genes involved in cholesterol and fatty acid biosynthesis (Ouimet et al., 2015). The co-expression of miR-33 with SREBP genes creates a coordinated regulatory program: when cellular cholesterol is low, SREBP2 is activated to increase cholesterol synthesis, and simultaneously, miR-33a is expressed to suppress ABCA1 and ABCG1, reducing cholesterol efflux and retaining cholesterol within the cell (Ouimet et al., 2015). Conversely, when cholesterol is abundant, SREBP2 and miR-33a are suppressed, allowing increased ABCA1/ABCG1 expression and cholesterol efflux (Ouimet et al., 2015).

Inhibition of miR-33 with antisense oligonucleotides (anti-miR-33) increases ABCA1 and ABCG1 expression in macrophages, enhances cholesterol efflux, and reduces foam cell formation (Rayner et al., 2011). In mouse models of atherosclerosis, systemic delivery of anti-miR-33 increases circulating HDL cholesterol by up to 37%, enhances RCT by up to 80%, and reduces atherosclerotic plaque size and lipid content (Rayner et al., 2011). Importantly, anti-miR-33 treatment also promotes macrophage polarization toward the M2 phenotype, with increased expression of Arg1, FIZZ1, IL-10, and IL-4, and decreased expression of TNF-α and IL-1β (Rayner et al., 2011). These findings demonstrate that miR-33 inhibition exerts dual beneficial effects on cholesterol metabolism and inflammation, positioning it as a promising therapeutic strategy for atherosclerosis (Rayner et al., 2011; Ouimet et al., 2015) (figure 4).

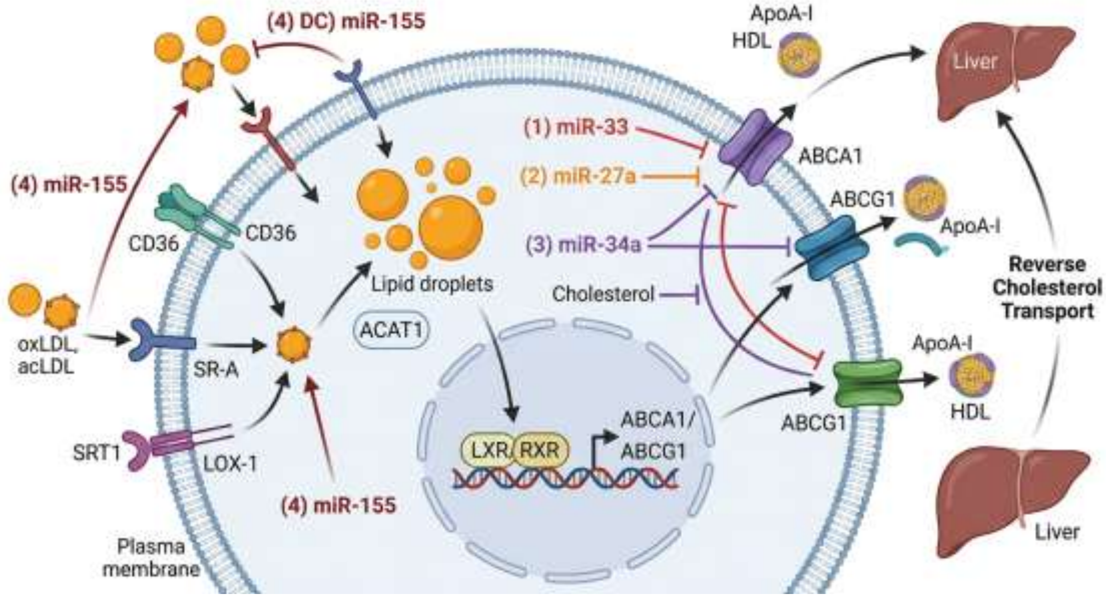

Figure 4. Regulation of cholesterol uptake, ABCA1/ABCG1-mediated efflux, reverse cholesterol transport, and foam-cell formation by microRNAs.

7. MICRORNAS IN ATHEROSCLEROTIC PLAQUE DEVELOPMENT

Atherosclerotic plaque development is a dynamic process involving multiple cell types, including endothelial cells, smooth muscle cells, macrophages, T cells, and platelets, each contributing to plaque initiation, progression, and complications (Zhan et al., 2026). MicroRNAs regulate gene expression in all of these cell types and mediate intercellular communication through extracellular vesicles, positioning them as master coordinators of plaque biology (Bouchareychas et al., 2020; Zhou et al., 2023).

In early atherosclerosis, endothelial dysfunction and monocyte recruitment are regulated by miRNAs including miR-126, miR-21, and miR-328-5p (Bouchareychas et al., 2020; Wu et al., 2024; Zhang et al., 2024). Endothelial miR-126 promotes vascular integrity and reduces inflammation, with loss of miR-126 exacerbating atherosclerosis (Bouchareychas et al., 2020). Conversely, endothelial miR-21 promotes inflammation through the SKP2/EP300/HMGB1 pathway, indirectly driving macrophage M1 polarization (Wu et al., 2024). miR-328-5p functions as a critical negative regulator in early endothelial inflammation, with its dysregulation contributing to advanced atherosclerosis (Zhang et al., 2024).

As plaques progress, macrophage accumulation and foam cell formation become dominant features, regulated by miRNAs including miR-33, miR-223, and miR-155 (Ouimet et al., 2015; Circulation Research, 2022; Nazari-Jahantigh et al., 2012). miR-33 suppresses cholesterol efflux and promotes foam cell formation, while miR-223 enhances efflux and reduces lipid accumulation (Ouimet et al., 2015; Circulation Research, 2022). The balance between these opposing miRNAs determines macrophage lipid content and foam cell burden (Ouimet et al., 2015). miR-155 amplifies inflammation in lesional macrophages, contributing to plaque progression and instability (Nazari-Jahantigh et al., 2012).

Smooth muscle cell migration from the media to the intima and their phenotypic switching from contractile to synthetic phenotype contribute to fibrous cap formation and plaque stability (Zhan et al., 2026). While the current review focuses on macrophage-centric miRNA regulation, it is important to note that miRNAs also regulate smooth muscle cell phenotype and function in atherosclerosis (Zhan et al., 2026). Comprehensive understanding of plaque biology requires integration of miRNA functions across all relevant cell types (Zhan et al., 2026).

Plaque vulnerability and rupture risk are determined by the balance between inflammatory and reparative processes, with M1 macrophages promoting instability and M2 macrophages supporting stability (Rayner et al., 2011). MicroRNAs that shift the M1/M2 balance, such as miR-146a, miR-181b, and miR-126, influence plaque stability and rupture risk (Wan et al., 2026; An et al., 2017; Zhan et al., 2026). Therapeutic delivery of M2-promoting miRNAs to vulnerable plaques represents a promising strategy for stabilizing high-risk lesions and preventing acute cardiovascular events (Wan et al., 2026; Li et al., 2025).

Macrophage-derived exosomes serve as vehicles for intercellular miRNA transfer and play important roles in plaque biology (Bouchareychas et al., 2020). IL-4-stimulated macrophages release exosomes enriched in anti-inflammatory miRNAs that can reprogram recipient macrophages toward M2 phenotype and modulate hematopoiesis, reducing monocyte production and lesion macrophage content (Bouchareychas et al., 2020). These findings reveal that macrophages not only respond to miRNA regulation but also actively shape the miRNA landscape of atherosclerotic lesions through exosome secretion (Bouchareychas et al., 2020).

The spatial and temporal dynamics of miRNA expression during plaque development remain incompletely understood. Advanced techniques including single-cell RNA sequencing and spatial transcriptomics are beginning to reveal the heterogeneity of miRNA expression within plaques and how this heterogeneity relates to plaque structure and stability (Zhan et al., 2026). Future studies employing these technologies will provide higher-resolution maps of miRNA function in atherosclerosis and may identify novel therapeutic targets (Zhan et al., 2026).

8. MICRORNAS AS CARDIOVASCULAR BIOMARKERS

Circulating miRNAs have emerged as promising biomarkers for cardiovascular disease, offering potential advantages over traditional biomarkers including high stability in blood, tissue-specific expression patterns, and dynamic regulation in response to pathological processes (Zaidi et al., 2025). MicroRNAs are present in circulation in multiple forms, including within extracellular vesicles (exosomes and microvesicles), bound to AGO proteins, or associated with lipoproteins, which protect them from degradation by RNases (Bouchareychas et al., 2020; Zhou et al., 2023).

Several miRNAs have been identified as candidate biomarkers for atherosclerosis and acute cardiovascular events. miR-155, miR-21, and miR-133a are elevated in circulation and in macrophage-derived exosomes in patients with atherosclerosis and myocardial infarction (Bouchareychas et al., 2020). miR-155 levels correlate with plaque inflammation and instability, suggesting potential utility for identifying high-risk patients (Fitzsimons et al., 2020). During atherosclerosis regression induced by lipid-lowering therapy, miR-155 levels decrease in urinary extracellular vesicles, indicating that miRNA biomarkers may also monitor therapeutic responses (Fitzsimons et al., 2020).

A systematic review of circulating miRNAs for ischemic heart disease identified multiple candidate biomarkers across diverse patient cohorts, but also highlighted significant heterogeneity in study design, assay protocols, and reproducibility (Zaidi et al., 2025). Variability in sample collection, processing, normalization strategies, and detection platforms contributes to inconsistent results across studies (Zaidi et al., 2025). Standardization of pre-analytical and analytical procedures is essential for translating circulating miRNA biomarkers into clinical practice (Zaidi et al., 2025).

Exosomal miRNAs may offer advantages over total circulating miRNAs as biomarkers, as they reflect active cellular secretion rather than passive release from damaged cells (Bouchareychas et al., 2020). Foam cell-derived exosomes containing specific miRNAs have been linked to plaque vulnerability in patients with large-artery atherosclerosis and ischemic stroke, suggesting that exosomal miRNA profiles may provide insights into plaque composition and rupture risk (Zhou et al., 2023). However, isolation and characterization of exosomes from clinical samples remain technically challenging and require further optimization (Zhou et al., 2023).

The integration of circulating miRNA biomarkers with traditional risk factors, imaging modalities, and other molecular biomarkers may improve cardiovascular risk stratification and enable personalized therapeutic strategies (Zaidi et al., 2025). Machine learning approaches that analyze multi-miRNA signatures rather than individual miRNAs may enhance diagnostic and prognostic accuracy (Zaidi et al., 2025). Prospective clinical studies with standardized protocols and large patient cohorts are needed to validate circulating miRNA biomarkers and establish their clinical utility (Zaidi et al., 2025).

Beyond diagnosis and prognosis, circulating miRNAs may serve as pharmacodynamic biomarkers to monitor responses to miRNA-based therapeutics (Euler et al., 2025). Changes in target miRNA levels or downstream effector molecules following therapeutic intervention could provide early indicators of efficacy and guide dose optimization (Euler et al., 2025). The development of companion diagnostics that measure circulating miRNAs alongside miRNA therapeutics represents an important goal for precision cardiovascular medicine (Euler et al., 2025).

9. THERAPEUTIC TARGETING OF MICRORNAS

9.1 MicroRNA Mimics

MicroRNA mimics are synthetic double-stranded RNA molecules designed to restore the function of endogenous miRNAs that are downregulated or deficient in disease states (Euler et al., 2025). Mimics are typically 19-25 nucleotides in length and incorporate chemical modifications to enhance stability, reduce immunogenicity, and improve pharmacokinetic properties (Euler et al., 2025). Upon cellular uptake, one strand of the mimic is loaded into the RISC complex, where it functions analogously to the endogenous miRNA to regulate target gene expression (Euler et al., 2025).

In atherosclerosis, miRNA mimics have been explored to restore anti-inflammatory and atheroprotective miRNAs that are reduced in lesional macrophages. Delivery of miR-146a mimics using a ROS-scavenger co-loaded nanogel achieved macrophage reprogramming toward M2 phenotype and significant reduction in plaque inflammation in preclinical models (Wan et al., 2026). This nanogel system combined miR-146a delivery with ROS scavenging to simultaneously address inflammatory signaling and oxidative stress (Wan et al., 2026). The nanogel was also engineered to be MRI-visible, enabling non-invasive monitoring of therapeutic delivery and distribution within atherosclerotic lesions (Wan et al., 2026).

The design of effective miRNA mimics requires careful consideration of chemical modifications to balance stability, potency, and safety (Euler et al., 2025). Common modifications include 2'-O-methyl (2'-OMe), 2'-O-methoxyethyl (2'-MOE), and locked nucleic acid (LNA) substitutions, which increase resistance to nuclease degradation and enhance binding affinity to target mRNAs (Euler et al., 2025). However, excessive modifications can reduce RISC loading efficiency or alter target specificity, necessitating empirical optimization for each miRNA mimic (Euler et al., 2025).

A key challenge for miRNA mimic therapeutics is achieving sufficient intracellular delivery to lesional macrophages while minimizing off-target effects in other tissues (Wan et al., 2026). Naked oligonucleotides exhibit poor cellular uptake and rapid clearance from circulation, limiting their therapeutic efficacy (Euler et al., 2025). Advanced delivery systems, including lipid nanoparticles, polymeric nanoparticles, and exosomes, enhance cellular uptake and enable targeted delivery to specific cell types and tissues (Wan et al., 2026; Zhou et al., 2023). These delivery technologies are discussed in detail in Section 9.3.

9.2 Antagomirs and Antisense Inhibitors

Antagomirs and antisense oligonucleotides are complementary sequences designed to bind and inhibit pathogenic miRNAs that are upregulated in disease (Euler et al., 2025). These molecules function by sequestering the target miRNA, preventing its loading into RISC and thereby relieving repression of target mRNAs (Euler et al., 2025). Antagomirs typically incorporate extensive chemical modifications, including 2'-OMe or LNA substitutions and phosphorothioate backbones, to enhance stability and binding affinity (Euler et al., 2025).

Inhibition of miR-33 with antisense oligonucleotides represents one of the most extensively studied miRNA therapeutic strategies for atherosclerosis. Systemic delivery of anti-miR-33 in Ldlr-/- mice with established atherosclerotic plaques increased circulating HDL cholesterol by 37%, enhanced RCT by up to 80%, and reduced plaque size and lipid content (Rayner et al., 2011). Importantly, anti-miR-33 treatment promoted macrophage polarization toward the M2 phenotype, with increased expression of Arg1, FIZZ1, IL-10, and IL-4, and decreased expression of TNF-α and IL-1β (Rayner et al., 2011). These dual effects on cholesterol metabolism and inflammation demonstrate the therapeutic potential of miR-33 inhibition (Rayner et al., 2011; Ouimet et al., 2015).

Local delivery of antagomirs to atherosclerotic lesions may enhance efficacy while reducing systemic exposure and off-target effects. Local application of an miR-342-5p antagomir to partially ligated carotid arteries inhibited atherosclerosis development in ApoE-/- mice, demonstrating proof-of-concept for site-specific miRNA inhibition (Wei et al., 2013). However, local delivery approaches face practical challenges for clinical translation, as atherosclerotic plaques are distributed throughout the arterial tree and are not amenable to direct injection (Wei et al., 2013).

An alternative approach is to engineer antagomirs with targeting moieties that direct them to specific cell types or tissues. Conjugation of antagomirs to antibodies, peptides, or aptamers that recognize cell-surface markers on macrophages or endothelial cells could enable selective delivery to atherosclerotic lesions (Euler et al., 2025). Inflammatory macrophage-targeted nanomedicine platforms that deliver anti-inflammatory miRNA cargo to plaques represent an advanced implementation of this strategy (Li et al., 2025). These systems combine targeting ligands, imaging agents, and therapeutic payloads to achieve theranostic functionality (Li et al., 2025).

9.3 Nanoparticle and Exosome Delivery Systems

Effective delivery of miRNA therapeutics to target cells and tissues represents a major challenge for clinical translation (Euler et al., 2025). Naked oligonucleotides exhibit poor cellular uptake due to their negative charge and hydrophilicity, and are rapidly cleared from circulation by renal filtration and nuclease degradation (Euler et al., 2025). Delivery systems that protect miRNA therapeutics from degradation, enhance cellular uptake, and enable targeted delivery to specific cell types are essential for achieving therapeutic efficacy (Wan et al., 2026; Li et al., 2025).

Lipid nanoparticles (LNPs) are among the most clinically advanced delivery systems for nucleic acid therapeutics, as demonstrated by their use in COVID-19 mRNA vaccines (Euler et al., 2025). LNPs consist of ionizable lipids, phospholipids, cholesterol, and polyethylene glycol (PEG)-lipids that self-assemble into particles that encapsulate and protect nucleic acids (Euler et al., 2025). Ionizable lipids facilitate endosomal escape following cellular uptake, enabling cytoplasmic delivery of the therapeutic payload (Euler et al., 2025). LNPs can be engineered with targeting ligands to direct them to specific cell types, including macrophages (Euler et al., 2025).

Polymeric nanoparticles offer additional versatility in terms of composition, size, surface properties, and release kinetics (Wan et al., 2026). A recent study developed a miRNA and ROS-scavenger co-loaded nanogel for atherosclerosis treatment (Wan et al., 2026). This nanogel delivered miR-146a-5p to reprogram macrophages toward M2 phenotype while simultaneously scavenging ROS to reduce oxidative stress (Wan et al., 2026). The nanogel was also engineered to be MRI-visible through incorporation of gadolinium, enabling non-invasive monitoring of therapeutic delivery and distribution within atherosclerotic lesions (Wan et al., 2026). In preclinical studies, this nanogel achieved significant reduction in plaque inflammation and improved plaque stability (Wan et al., 2026).

Another advanced platform is inflammatory macrophage-targeted nanomedicine that delivers anti-inflammatory miRNA cargo to plaques with concurrent MRI visualization (Li et al., 2025). This system incorporates targeting ligands that recognize markers on inflammatory macrophages, such as scavenger receptors or integrin receptors, enabling selective accumulation in atherosclerotic lesions (Li et al., 2025). The integration of imaging and therapeutic functions in a single platform—termed theranostics—allows real-time monitoring of drug delivery and therapeutic responses (Li et al., 2025).

Exosomes, naturally occurring extracellular vesicles secreted by cells, represent an alternative delivery platform with potential advantages including biocompatibility, low immunogenicity, and intrinsic targeting properties (Zhou et al., 2023; Bouchareychas et al., 2020). Exosomes can be loaded with miRNA therapeutics through electroporation, transfection, or by engineering donor cells to overexpress the desired miRNA (Zhou et al., 2023). Macrophage-derived exosomes enriched in anti-inflammatory miRNAs have been shown to resolve atherosclerosis by reprogramming recipient macrophages and modulating hematopoiesis (Bouchareychas et al., 2020). Adipose-derived stem cell exosomes containing miRNAs that modulate cholesterol efflux and inflammation also show promise for atherosclerosis treatment (Zhou et al., 2023).

Despite these advances, significant challenges remain for clinical translation of nanoparticle and exosome delivery systems. These include optimizing biodistribution to maximize lesion accumulation while minimizing off-target delivery, ensuring long-term safety and lack of toxicity, scaling up manufacturing processes to produce clinical-grade materials, and navigating regulatory pathways for approval (Euler et al., 2025; Wan et al., 2026). Addressing these challenges will require continued collaboration between academic researchers, pharmaceutical companies, and regulatory agencies (Euler et al., 2025) (figure 5).

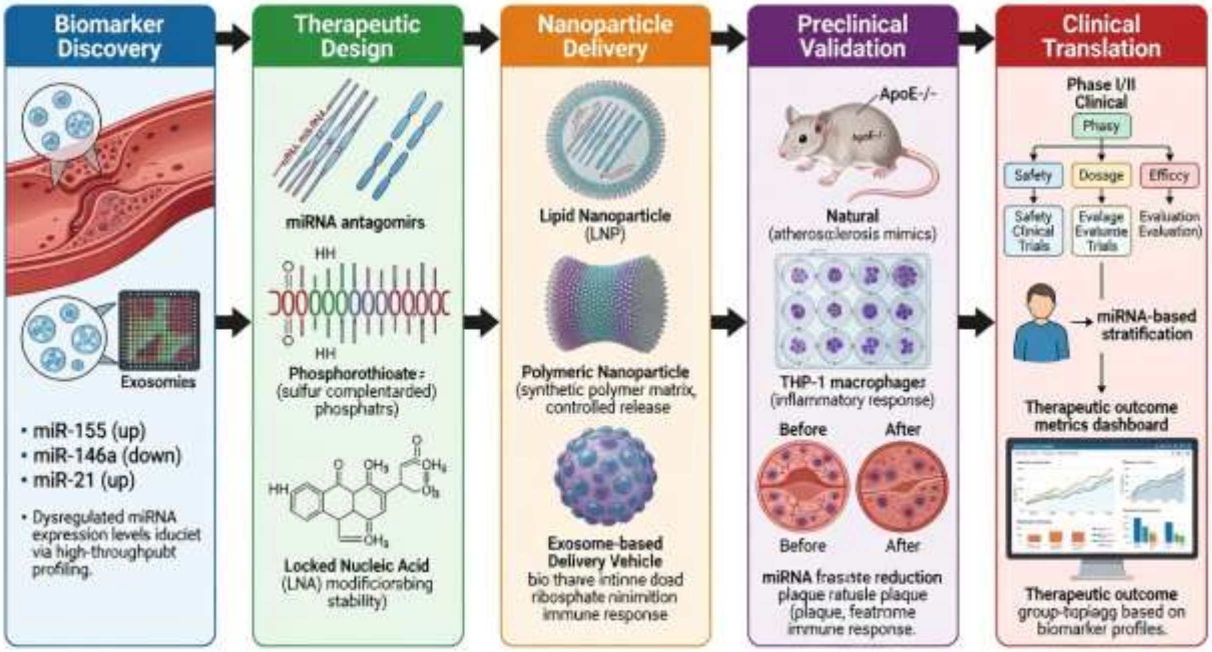

Figure 5. Translational model of microRNA-targeted therapeutics in atherosclerosis including biomarkers, antagomirs, mimics, nanoparticle delivery, and precision medicine applications.

10. CURRENT LIMITATIONS AND KNOWLEDGE GAPS

Despite significant advances in understanding miRNA regulation of macrophage polarization in atherosclerosis, important limitations and knowledge gaps remain (Zhan et al., 2026). A primary limitation is that most mechanistic studies have been conducted in vitro using cultured macrophages or in vivo using mouse models, with limited validation in human lesional macrophages (Zhan et al., 2026). While mouse models have provided valuable insights, important differences exist between mouse and human atherosclerosis, including lesion composition, plaque stability, and immune cell populations (Zhan et al., 2026). Direct studies of miRNA expression and function in human atherosclerotic plaques are needed to confirm the translational relevance of findings from model systems (Zhan et al., 2026).

The identification of direct miRNA-target relationships in the context of atherosclerosis remains incomplete. While computational algorithms predict hundreds of potential targets for each miRNA based on seed sequence complementarity, experimental validation of these predictions in lesional macrophages is limited (Euler et al., 2025). Many studies rely on reporter assays or overexpression systems that may not accurately reflect endogenous miRNA-target interactions in the complex microenvironment of atherosclerotic plaques (Euler et al., 2025). Techniques such as crosslinking and immunoprecipitation of AGO proteins followed by sequencing (CLIP-seq) can identify bona fide miRNA-target interactions in specific cell types and disease contexts, but have been applied to atherosclerosis in only a limited number of studies (Euler et al., 2025).

The spatial and temporal dynamics of miRNA expression during atherosclerosis progression and regression remain poorly characterized. Atherosclerotic plaques are heterogeneous structures containing multiple cell types with distinct spatial distributions, and miRNA expression likely varies across different plaque regions (Zhan et al., 2026). Single-cell RNA sequencing and spatial transcriptomics technologies are beginning to reveal this heterogeneity, but comprehensive atlases of miRNA expression in human plaques at single-cell resolution are not yet available (Zhan et al., 2026). Understanding how miRNA expression changes during plaque progression, stabilization, and regression will be essential for identifying optimal therapeutic windows and strategies (Fitzsimons et al., 2020).

For several miRNAs discussed in this review, including miR-27a, miR-24, and miR-145, the available literature does not provide sufficient evidence to establish validated primary targets or mechanistic pathways in macrophage polarization or atherosclerosis. While these miRNAs have been implicated in cardiovascular disease in some studies, the lack of robust mechanistic data limits conclusions about their specific roles and therapeutic potential (Zhan et al., 2026). Future research should prioritize rigorous mechanistic studies to elucidate the functions of these and other incompletely characterized miRNAs in atherosclerosis (Zhan et al., 2026).

The regulation of cholesterol uptake receptors, including SR-A, CD36, and LOX-1, by miRNAs remains an understudied area. While miRNA regulation of cholesterol efflux pathways (ABCA1, ABCG1) has been extensively characterized, direct evidence for miRNA control of scavenger receptor expression in macrophages is limited (Zhan et al., 2026). Given that foam cell formation results from the imbalance between cholesterol uptake and efflux, therapeutic strategies that simultaneously reduce uptake and enhance efflux may be more effective than targeting efflux alone (Zhan et al., 2026). Identifying miRNAs that regulate scavenger receptors represents an important research priority (Zhan et al., 2026).

The standardization of circulating miRNA biomarker studies remains a significant challenge. Variability in sample collection, processing, RNA extraction, normalization strategies, and detection platforms contributes to inconsistent results across studies and limits clinical translation (Zaidi et al., 2025). International efforts to establish standardized protocols for circulating miRNA biomarker studies, similar to those developed for other biomarkers, are urgently needed (Zaidi et al., 2025). Additionally, large-scale prospective clinical studies with well-defined patient cohorts and clinical endpoints are required to validate candidate biomarkers and establish their clinical utility (Zaidi et al., 2025).

Finally, the long-term safety and efficacy of miRNA therapeutics for atherosclerosis remain to be established. While short-term preclinical studies have demonstrated promising results, the chronic nature of atherosclerosis requires long-term treatment, and the consequences of sustained miRNA modulation over years or decades are unknown (Euler et al., 2025). Potential concerns include development of resistance, compensatory upregulation of alternative pathways, off-target effects that manifest only with prolonged exposure, and immunological responses to repeated administration (Euler et al., 2025). Comprehensive long-term preclinical studies and carefully designed clinical trials will be essential for addressing these questions (Euler et al., 2025).

11. FUTURE DIRECTIONS

The field of miRNA regulation of macrophage polarization in atherosclerosis is poised for significant advances in the coming years, driven by technological innovations and increasing translational focus (Zhan et al., 2026). Several key research directions hold particular promise for advancing mechanistic understanding and therapeutic development (Euler et al., 2025; Zaidi et al., 2025).

Single-cell and spatial transcriptomics technologies will enable comprehensive mapping of miRNA expression across different cell types and spatial regions within atherosclerotic plaques (Zhan et al., 2026). These approaches will reveal the heterogeneity of macrophage populations in plaques, identify distinct macrophage subsets with unique miRNA signatures, and elucidate how miRNA expression relates to cellular phenotype and spatial localization (Zhan et al., 2026). Integration of single-cell miRNA profiling with single-cell mRNA sequencing and proteomics will provide systems-level understanding of miRNA regulatory networks in atherosclerosis (Zhan et al., 2026).

Advanced imaging technologies that enable visualization of miRNA expression and activity in living animals will facilitate longitudinal studies of miRNA dynamics during atherosclerosis progression and regression (Li et al., 2025). Molecular imaging probes that report on miRNA activity, combined with MRI, PET, or optical imaging modalities, could enable non-invasive monitoring of disease processes and therapeutic responses (Li et al., 2025; Wan et al., 2026). The development of theranostic platforms that integrate imaging and therapeutic functions represents a particularly promising direction for personalized medicine (Li et al., 2025).

Combinatorial miRNA therapeutic strategies that simultaneously modulate multiple miRNAs may achieve more robust and sustained effects than single-miRNA approaches (Zhan et al., 2026). For example, combining miR-33 inhibition to enhance cholesterol efflux with miR-146a delivery to suppress inflammation could address multiple pathogenic mechanisms simultaneously (Rayner et al., 2011; Wan et al., 2026). Rational design of combination therapies will require comprehensive understanding of miRNA network interactions and potential synergistic or antagonistic effects (Zhan et al., 2026).

The integration of miRNA therapeutics with other treatment modalities, including lipid-lowering drugs, anti-inflammatory agents, and immunomodulatory therapies, represents another important direction (Euler et al., 2025). MicroRNA-based interventions may enhance the efficacy of existing therapies or enable dose reduction to minimize side effects (Euler et al., 2025). Clinical trials evaluating miRNA therapeutics in combination with standard-of-care treatments will be essential for establishing optimal therapeutic regimens (Euler et al., 2025).

Personalized medicine approaches that tailor miRNA therapeutics to individual patient characteristics hold significant promise (Zaidi et al., 2025). Genetic variants affecting miRNA biogenesis, target recognition, or expression levels may influence therapeutic responses and could be used for patient stratification (Zaidi et al., 2025). Circulating miRNA biomarkers could identify patients with specific pathogenic mechanisms that are most likely to benefit from targeted miRNA interventions (Zaidi et al., 2025). The development of companion diagnostics that guide patient selection and dose optimization will be critical for realizing the potential of precision miRNA therapeutics (Euler et al., 2025).

Expanding the therapeutic toolkit beyond traditional mimics and antagomirs represents an exciting frontier. Emerging approaches include small molecule modulators of miRNA biogenesis or function, CRISPR-based technologies for precise editing of miRNA genes or target sites, and engineered RNA-binding proteins that selectively modulate specific miRNA-target interactions (Euler et al., 2025). These next-generation tools may offer advantages in terms of specificity, durability, and ease of delivery compared to oligonucleotide-based approaches (Euler et al., 2025).

Finally, translational research that bridges the gap between preclinical discoveries and clinical applications must remain a priority. This includes conducting rigorous preclinical studies in large animal models that more closely recapitulate human atherosclerosis, establishing good manufacturing practices for clinical-grade miRNA therapeutics and delivery systems, and designing well-powered clinical trials with appropriate endpoints and patient populations (Euler et al., 2025). Collaboration between academic researchers, pharmaceutical companies, regulatory agencies, and patient advocacy groups will be essential for advancing miRNA therapeutics from bench to bedside (Euler et al., 2025).

12. CONCLUSION

MicroRNAs have emerged as master regulators of macrophage polarization and function in atherosclerosis, controlling complex gene expression networks that determine cellular phenotype, inflammatory responses, and lipid metabolism (Zhan et al., 2026). This review has synthesized current evidence demonstrating that specific miRNAs promote M1 pro-inflammatory polarization (miR-155, miR-21, miR-342-5p) or M2 anti-inflammatory polarization (miR-223, miR-146a, miR-126, miR-181b), with profound consequences for atherosclerotic plaque development and stability (Nazari-Jahantigh et al., 2012; Wu et al., 2024; Wei et al., 2013; Circulation Research, 2022; Wan et al., 2026; Bouchareychas et al., 2020; An et al., 2017).

A central theme emerging from the literature is the integration of miRNA regulation across multiple pathogenic mechanisms in atherosclerosis. miR-33 exemplifies this integration, simultaneously suppressing cholesterol efflux through targeting of ABCA1 and ABCG1, inhibiting fatty acid oxidation, and promoting M1 polarization, thereby coordinating lipid metabolism and inflammation (Ouimet et al., 2015; Rayner et al., 2011). Conversely, miR-223 promotes both cholesterol efflux and anti-inflammatory responses, demonstrating that single miRNAs can exert pleiotropic atheroprotective effects (Circulation Research, 2022). These findings highlight the potential of miRNA-based therapeutics to address multiple disease mechanisms simultaneously, an advantage over traditional single-target drugs (Zhan et al., 2026).

The therapeutic potential of miRNA modulation has been demonstrated in numerous preclinical studies. Inhibition of miR-33 with antisense oligonucleotides increases HDL cholesterol, enhances reverse cholesterol transport, promotes M2 macrophage polarization, and reduces atherosclerotic plaque burden in mouse models (Rayner et al., 2011). Delivery of miR-146a mimics using advanced nanoparticle systems reprograms lesional macrophages toward anti-inflammatory phenotype and reduces plaque inflammation (Wan et al., 2026). Inflammatory macrophage-targeted nanomedicine platforms that combine miRNA therapeutics with imaging capabilities enable theranostic approaches for atherosclerosis treatment (Li et al., 2025). These proof-of-concept studies establish the feasibility of miRNA-based interventions for cardiovascular disease (Euler et al., 2025).

Circulating miRNAs show promise as non-invasive biomarkers for cardiovascular risk assessment, disease monitoring, and therapeutic response evaluation (Zaidi et al., 2025). However, significant challenges remain in standardizing assay protocols, validating biomarkers in large prospective cohorts, and establishing clinical utility (Zaidi et al., 2025). The integration of circulating miRNA biomarkers with miRNA therapeutics could enable precision medicine approaches that match patients to optimal treatments and monitor therapeutic efficacy in real time (Euler et al., 2025).

Despite these advances, important limitations and knowledge gaps must be addressed before miRNA therapeutics can be translated to clinical practice. These include achieving delivery specificity to lesional macrophages, minimizing off-target effects, validating findings from mouse models in human disease, establishing long-term safety and efficacy, and navigating regulatory pathways (Euler et al., 2025; Zhan et al., 2026). The development of advanced delivery systems, including targeted nanoparticles and exosomes, represents significant progress toward overcoming delivery challenges (Wan et al., 2026; Li et al., 2025; Zhou et al., 2023).

Looking forward, the field is poised for transformative advances driven by single-cell and spatial transcriptomics, advanced imaging technologies, combinatorial therapeutic strategies, and personalized medicine approaches (Zhan et al., 2026; Euler et al., 2025). The integration of miRNA therapeutics with existing cardiovascular treatments may enhance efficacy and enable new therapeutic paradigms (Euler et al., 2025). Continued collaboration between basic researchers, translational scientists, clinicians, pharmaceutical companies, and regulatory agencies will be essential for realizing the full therapeutic potential of miRNA-based interventions for atherosclerosis and cardiovascular disease (Euler et al., 2025).

In conclusion, miRNAs represent a new frontier in cardiovascular medicine, offering unprecedented opportunities to reprogram macrophage phenotype, modulate inflammation, enhance cholesterol efflux, and stabilize vulnerable plaques. While significant challenges remain, the rapid pace of technological innovation and increasing translational focus suggest that miRNA-based diagnostics and therapeutics will play important roles in the future management of atherosclerotic cardiovascular disease.

Author Contributions

Author Contributions Statement: S.R is responsible for literature search, synthesis, critical analysis, and editorial preparation.

Conflict of Interest

Conflict of Interest Statement: The author declares no conflict of interest. The author has no financial relationships, commercial interests, or personal affiliations that could have influenced the design, conduct, or reporting of this review.

Funding

Funding Statement: This review received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. No external funding was used in the preparation of this manuscript.

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