Gene Expression **2025** vol. 24(3) | 219–234
DOI: 10.14218/GE.2025.00010

Review Article

MicroRNAs in the Regulation of Immune Response in Cardiovascular Diseases: New Diagnostic and Therapeutic Tools

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Received: January 23, 2025 | **Revised:** March 07, 2025 | **Accepted:** March 26, 2025 | **Published online:** April 23, 2025

Abstract

Cardiovascular diseases (CVDs) remain the leading cause of global morbidity and mortality, highlighting the urgent need for innovative diagnostic and prognostic approaches to address their complex pathophysiology. Recent advances in molecular cardiology have unveiled immune-derived microRNAs (miRNAs), or immuno-miRs, as pivotal regulators in the interplay between immune responses and cardiovascular pathology. Secreted by immune cells such as T lymphocytes, macrophages, and neutrophils, these small non-coding RNAs modulate critical signaling pathways by regulating gene expression. Immuno-miRs influence essential processes, including inflammation, endothelial dysfunction, and fibrotic remodeling—core mechanisms underlying conditions such as atherosclerosis, myocardial infarction, and heart failure. Moreover, their presence in systemic circulation within extracellular vesicles underscores their role in intercellular communication, impacting both immune and non-immune cardiovascular cells, such as cardiomyocytes and endothelial cells. This dual functionality renders immuno-miRs promising candidates as diagnostic biomarkers for early disease detection and as prognostic tools for assessing disease progression and therapeutic efficacy. Furthermore, emerging miRNA-based interventions—such as miRNA mimics and inhibitors—show considerable promise in modulating immune dysregulation in CVDs, although clinical translation remains a significant challenge. In this review, we comprehensively examine the regulatory roles of immuno-miRs in both innate and adaptive immune responses and explore recent advancements in miRNA-based therapies. By consolidating current knowledge and identifying existing gaps, we provide a comprehensive overview of the transformative potential of immuno-miRs in CVD management. Integrating these molecules into personalized medicine may pave the way for more effective, targeted, and minimally invasive strategies to combat one of the world's most pressing health challenges.

Introduction

Cardiovascular diseases (CVDs) are a leading cause of global mortality, accounting for approximately 18.6 million deaths annually—a number projected to rise due to increasing life expectancy, urbanization, and the growing prevalence of risk factors such as obesity, diabetes, and hypertension.[1] Despite advancements in pharmacological and interventional treatments, the complex pathophysiology of CVD remains a significant challenge. Central to this complexity is the interplay between the immune system and cardiovascular tissues, which plays a pivotal role in the initiation, progression, and resolution of these diseases.[2] The immune system, comprising innate and adaptive components, acts as a double-edged sword in cardiovascular health. While immune responses are essential for maintaining homeostasis and initiating tissue repair, their dysregulation can lead to chronic inflammation, fibrosis, and adverse remodeling—hallmark features of CVDs.[3] For instance, macrophages contribute both to the clearance of necrotic debris and the exacerbation of inflammation in myocardial infarction, whereas T cells are implicated in the destabilization of atherosclerotic plaques.[4] Understanding the mechanisms that govern these immune responses is critical for developing novel diagnostic and therapeutic strategies. In recent years, microRNAs (miRNAs) have emerged as key regulators

Keywords: Cardiovascular diseases; miRNAs; miR-155; Immuno-miRs; Immune system; Therapy; Diagnosis; Inflammation.

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How to cite this article: Gareev I, Beylerli O, Sufianov A, Gulieva L, Pavlov V, Shi H. MicroRNAs in the Regulation of Immune Response in Cardiovascular Diseases: New Diagnostic and Therapeutic Tools. *Gene Expr* 2025;24(3):219–234. doi: 10.14218/GE.2025.00010.

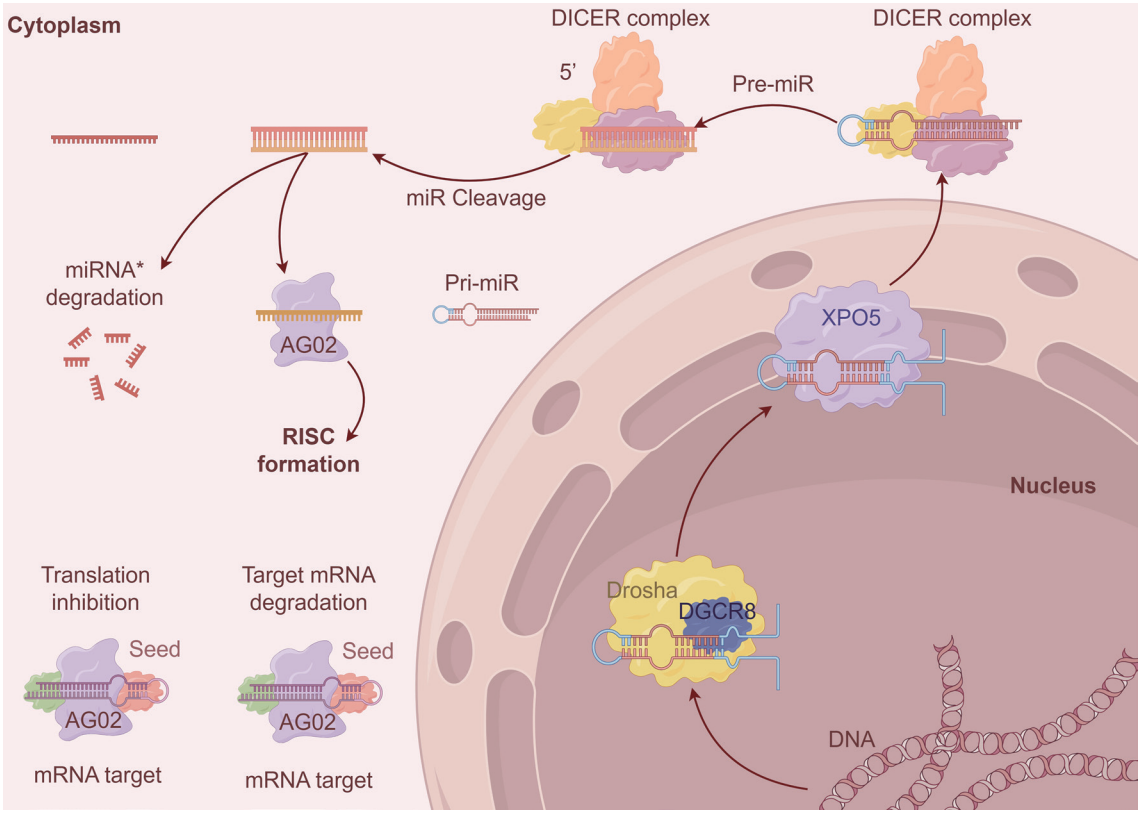

Fig. 1. Biogenesis of microRNA (miRNA). DGCR8, DiGeorge syndrome critical region 8; mRNA, messenger RNA; RISC, RNA-induced silencing complex.

of the crosstalk between the immune and cardiovascular systems. miRNAs are small, non-coding RNA molecules, typically 18–22 nucleotides in length, that regulate gene expression by binding to complementary sequences in the 3′-untranslated regions of target messenger RNAs (mRNAs) (Fig. 1).[5]

These molecules orchestrate a wide range of cellular processes, including apoptosis, differentiation, and immune modulation.[6] Immune-derived miRNAs, often referred to as "immuno-miRs", are a subset predominantly expressed in immune cells such as macrophages, T lymphocytes, B cells, and natural killer (NK) cells.[7] Their roles in CVD have garnered increasing attention due to their capacity to modulate inflammatory pathways and immune cell phenotypes. For example, miR-223—highly expressed in neutrophils and macrophages—acts as a critical regulator of myeloid cell differentiation and inflammatory responses, influencing atherosclerotic plaque formation and stability.[8] Similarly, miR-181a, a key player in T cell development and activation, has been shown to modulate immune aging, a factor contributing to the heightened risk of CVD in older adults.[9] One of the most promising aspects of immune-derived miRNAs lies in their potential as biomarkers. Circulating miRNAs, found either freely or encapsulated within extracellular vesicles such as exosomes, offer a stable and non-invasive means of assessing disease states. Their expression profiles can reflect underlying immune activity, providing insights into disease progression, severity, and treatment response.[10] For example, elevated levels of miR-21 and miR-155 in plasma have been correlated with adverse outcomes in heart failure and myocardial infarction, respectively, highlighting their diagnostic and prognostic value.[11] Moreover, immune-derived miRNAs represent a novel therapeutic frontier in CVD. Advances in RNA-based therapeutics have facilitated the development of miRNA mimics and inhibitors (antagomiRs) designed to restore normal gene expression patterns. Preclinical studies have demonstrated the efficacy of these approaches in reducing inflammation, promoting tissue repair, and improving cardiac function following myocardial infarction.[12] For instance, nanoparticle-based delivery systems targeting miR-21 in cardiac macrophages have shown promise in mitigating pathological remodeling and fibrosis.[13] Despite these advances, challenges such as off-target effects, delivery efficiency, and long-term safety remain significant barriers to clinical translation.[14] This review aimed to provide a comprehensive overview of the current understanding of immune-derived miRNAs in CVD. We will explore their roles in immune modulation, their potential as biomarkers for early diagnosis and risk stratification, and their therapeutic applications. By consolidating existing evidence and identifying gaps in knowledge, this work sought to support the integration of miRNAs into the field of precision cardiovascular medicine. Harnessing the potential of these molecules could revolutionize CVD management by offering more targeted, effective, and minimally invasive therapeutic strategies to address this global health burden.

miRNAs in immune cell development and function

miRNAs are essential non-coding RNAs that play pivotal roles in regulating the development, differentiation, activation, and function of immune cells. By fine-tuning gene expression through mRNA degradation or translational inhibition, miRNAs are critical for maintaining immune homeostasis and mounting appropriate responses to pathological stimuli.[15] Immune-derived miRNAs,

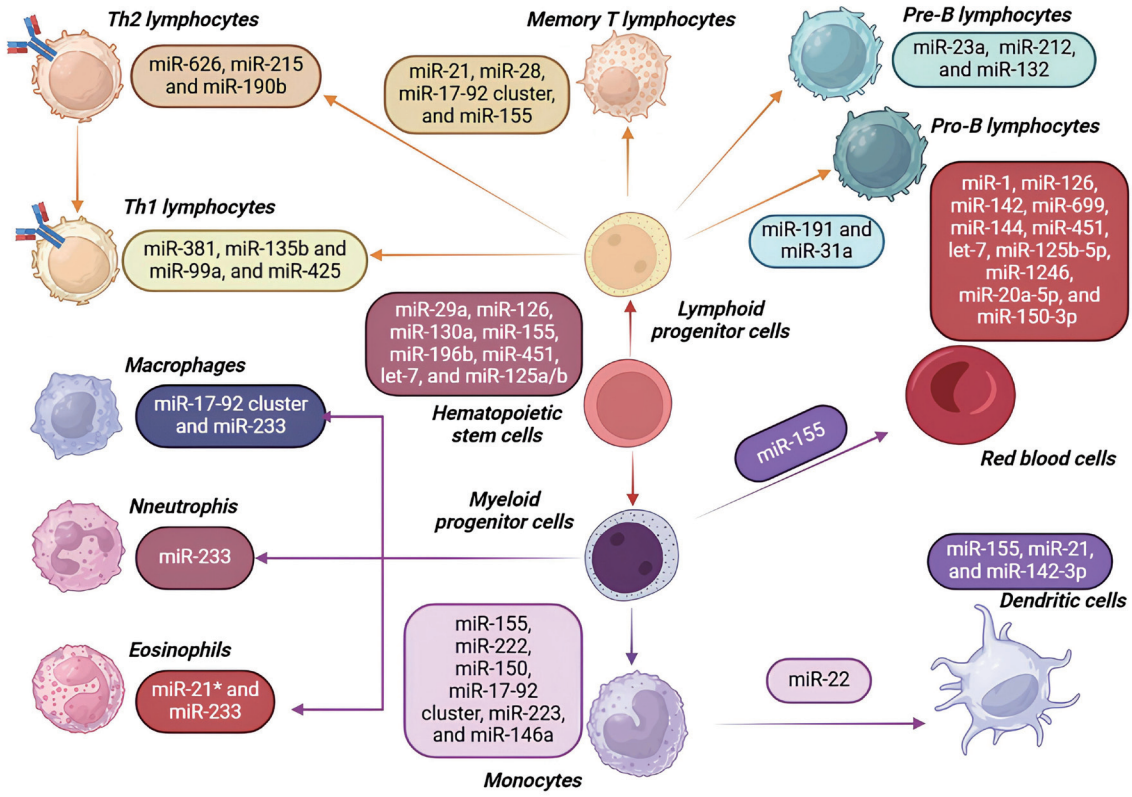

Fig. 2. Overview of immune cells and their regulatory microRNAs (miRNAs). Th1, type 1 T helper.

often termed "immuno-miRs", regulate both innate and adaptive immune responses, influencing processes such as inflammation, tissue repair, and immune tolerance. Dysregulation of these miRNAs has been increasingly linked to the pathogenesis of CVDs, emphasizing their dual role as both contributors to disease progression and potential therapeutic targets (Fig. 2).[16]

miRNAs in innate immune cells

Innate immune cells—including macrophages, neutrophils, and NK cells—are the body's first responders to tissue damage or infection. miRNAs regulate their development, polarization, and activation, shaping the balance between pro-inflammatory and anti-inflammatory responses. Macrophages, known for their plasticity, can polarize into pro-inflammatory M1 or anti-inflammatory M2 states depending on environmental cues. miR-223 is a key regulator of macrophage differentiation, preventing excessive inflammatory responses by targeting transcription factors such as nuclear factor I-A and other signal transducers.[17] Studies have demonstrated that miR-223 deficiency leads to unrestrained M1 macrophage activation, exacerbating inflammation in conditions such as atherosclerosis and myocardial infarction.[18] Another important miRNA, miR-155, is a well-characterized pro-inflammatory molecule that promotes M1 polarization by enhancing cytokine production—particularly tumor necrosis factor-alpha and interleukin-6—via activation of the nuclear factor kappa B (NF-κB) pathway.[19] Overexpression of miR-155 has been associated with chronic inflammatory diseases including heart failure and hypertension, where persistent macrophage activation contributes to tissue damage.[20] Neutrophils, another vital component of the innate immune response, also rely on miRNAs for proper function. miR-146a acts as a negative regulator of neutrophil-mediated inflammation by targeting key elements of Toll-like receptor (TLRs) and NF-κB signaling pathways, such as interleukin-1 receptor-associated kinase 1 (IRAK1) and tumor necrosis factor receptor-associated factor 6 (TRAF6).[21] Dysregulation of miR-146a can lead to exaggerated neutrophilic responses, frequently observed in acute myocardial infarction and other inflammatory conditions.[22] NK cells, which are essential for antiviral defense and tumor surveillance, are also regulated by miRNAs. miR-27a has been shown to modulate NK cell cytotoxicity by targeting genes involved in degranulation and cytokine release. Impaired miRNA expression in NK cells can compromise their function, contributing to the chronic inflammation seen in CVD.[23]

miRNAs in adaptive immune cells

In the adaptive immune system, miRNAs are indispensable for the regulation of T and B lymphocytes, ensuring proper immune activation and tolerance. T cells depend on miRNAs for both thymic development and peripheral activation. miR-181a is a master regulator of T cell receptor (TCR) sensitivity, fine-tuning the signaling threshold during positive and negative selection in the thymus. Reduced miR-181a expression in aged individuals has been associated with diminished T cell responsiveness, contributing to immune senescence and the increased risk of CVD in elderly populations.[24] The miR-17-92 cluster, a polycistronic group of miRNAs, is crucial for T cell survival and proliferation. Dysregulation of this cluster impairs effector and memory T cell responses, weakening immunity during chronic inflammation, as seen in atherosclerosis and myocardial infarction.[25] Regulatory T cells (Tregs) are critical for maintaining immune tolerance and preventing excessive

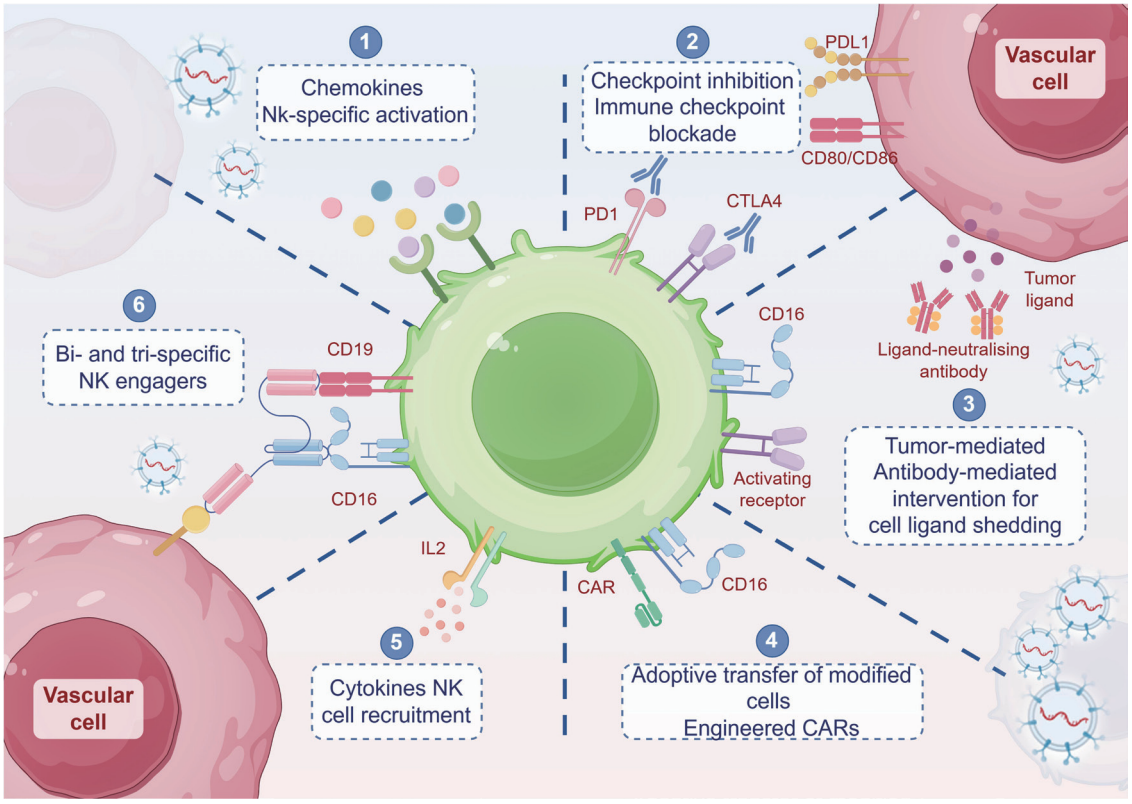

Fig. 3. miRNA-loaded extracellular vesicles (EVs) can be produced directly by T cells upon engagement with vascular cells. CARs, chimeric antigen receptors; CD, cluster of differentiation; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; IL, interleukin; NK, natural killer; PD1, programmed cell death 1; PDL1, programmed death-ligand 1.

inflammation. miR-142-3p and miR-142-5p regulate Treg function by modulating cyclic adenosine monophosphate signaling and transforming growth factor-beta (TGF-β) receptor expression, both of which are essential for Treg-mediated suppression of pro-inflammatory effector T cells.[26] Deletion of miR-142 disrupts Treg homeostasis, leading to widespread immune activation and tissue damage in models of hypertension and atherosclerosis.[27] B cells also rely on miRNAs for proper differentiation and antibody production. miR-150 is critical for the transition from precursor to mature B cells, while miR-34a regulates class-switch recombination and somatic hypermutation. Dysregulation of these miRNAs can impair humoral immunity, contributing to chronic inflammation and the production of autoantibodies often observed in autoimmune-associated CVD.[28]

miRNAs in immune cell crosstalk and extracellular vesicle communication

Beyond their intracellular functions, miRNAs are instrumental in intercellular communication via extracellular vesicles (EVs), such as exosomes. Immune cells, including macrophages and T cells, release miRNA-enriched EVs into circulation, influencing the activity of distant target cells (Fig. 3). For instance, EVs enriched with miR-223, secreted by macrophages, can downregulate inflammatory signaling in endothelial cells, offering protection against vascular damage.[29] Conversely, EVs containing miR-155 released during chronic inflammation can amplify pro-inflammatory responses in recipient cells, thereby accelerating atherosclerosis progression.[30] These findings highlight the dual role of miRNAs as both mediators and messengers of immune responses, making them attractive therapeutic targets for modulating immune cell communication in CVD.[31]

The regulatory functions of miRNAs in immune cells have profound implications for understanding and treating CVD. Their dysregulation contributes to disease pathophysiology while offering novel opportunities for therapeutic intervention. miRNA-based therapies—such as antagomiRs and miRNA mimics—have shown promise in restoring normal immune cell function in preclinical studies. For example, nanoparticle-mediated delivery of miR-21 to cardiac macrophages post-myocardial infarction has been shown to reduce fibrosis and improve cardiac function.[32] Furthermore, the stability of circulating miRNAs makes them valuable diagnostic and prognostic biomarkers, enabling minimally invasive monitoring of immune activity and disease progression.[33]

Immunity and CVD risk factors

CVDs are influenced by genetic and environmental factors, but also by complex interactions within the immune system. Chronic low-grade inflammation, driven by dysregulated immune responses, has emerged as a hallmark of major CVD risk factors, including obesity, hypertension, diabetes, and dyslipidemia.[34] The immune system modulates these risk factors through a network of innate and adaptive immune cells, cytokines, and miRNAs, which regulate inflammatory pathways and cellular communication. Understanding these interactions is crucial for identifying novel biomarkers and therapeutic targets for CVD prevention and management.

Obesity and adipose tissue inflammation

Obesity is a major risk factor for CVD and is often accompanied by chronic inflammation in adipose tissue. Once considered a passive fat reservoir, adipose tissue is now recognized as an active endocrine organ that produces pro-inflammatory cytokines and adipokines. In obesity, immune cells infiltrate adipose tissue, contributing to systemic inflammation and metabolic dysregulation.[35] Epicardial adipose tissue (EAT), a visceral fat depot surrounding the myocardium, has been implicated in the development of coronary artery disease and atrial fibrillation. Increased EAT volume correlates with heightened expression of inflammatory miRNAs, such as miR-34a and miR-103, which modulate macrophage polarization and Th2 chemokine signaling, respectively.[36] miR-34a promotes pro-inflammatory M1 macrophage activity, exacerbating local inflammation, while reduced miR-103 levels in EAT have been linked to impaired regulation of anti-inflammatory pathways.[37] Furthermore, miRNAs in exosomes secreted by adipocytes, such as miR-223 and miR-155, influence immune cell behavior in distant tissues. These miRNAs enhance inflammatory responses in macrophages and endothelial cells, contributing to vascular dysfunction and insulin resistance.[38]

Hypertension and immune dysregulation

Hypertension, a major CVD risk factor, is increasingly recognized as an immune-mediated disorder. Early research demonstrated that Rag1 knockout mice, which are deficient in T and B lymphocytes, are protected against angiotensin II-induced hypertension, implicating adaptive immune responses in the disease pathogenesis.[39] Subsequent studies have revealed specific miRNAs that regulate immune cells in hypertension. For instance, miR-214, which is upregulated in perivascular adipose tissue during angiotensin II-induced hypertension, amplifies vascular stiffening and fibrosis by modulating T cell activation and cytokine production.[40] Deletion of miR-214 reduces inflammation and vascular damage, highlighting its therapeutic potential. Similarly, miR-31 influences the balance between Treg and T helper 17 cells, with its deletion reducing hypertension, cardiac hypertrophy, and renal fibrosis in experimental models.[41] In addition to adaptive immune responses, innate immune cells such as monocytes and macrophages play critical roles in hypertension. miR-155, widely expressed in these cells, exacerbates vascular inflammation and remodeling by targeting transcriptional repressors of pro-inflammatory pathways.[42]

Diabetes and immune-driven inflammation

Diabetes is a significant CVD risk factor characterized by chronic systemic inflammation. Hyperglycemia and insulin resistance activate the immune system, leading to endothelial dysfunction and accelerated atherosclerosis. Immune cells, particularly macrophages, infiltrate pancreatic islets and vascular tissues, contributing to inflammation and tissue damage.[43] miRNAs regulate immune responses in diabetes-associated CVD. For instance, miR-146a mitigates inflammation by targeting IRAK1 and TRAF6 in macrophages, reducing cytokine production.[44] However, its downregulation in diabetic patients leads to unrestrained inflammation and vascular complications. Conversely, miR-21 is upregulated in diabetes, promoting fibrosis and endothelial dysfunction by enhancing TGF-β signaling pathways.[45]

Dyslipidemia and atherosclerosis

Dyslipidemia, characterized by elevated low-density lipoprotein levels and reduced high-density lipoprotein, is a major driver of atherosclerosis. Immune cells, particularly macrophages, play a central role in plaque formation and progression by engulfing oxidized low-density lipoprotein and forming foam cells. Dysregulated miRNAs contribute to this process by modulating lipid metabolism and inflammatory signaling. miR-33, a well-studied miRNA in dyslipidemia, suppresses cholesterol efflux from macrophages by targeting ATP-binding cassette transporter A1, leading to lipid accumulation and foam cell formation.[46] Inhibition of miR-33 enhances cholesterol efflux and reduces plaque burden in experimental models of atherosclerosis. Similarly, miR-155 promotes foam cell formation by enhancing macrophage inflammatory responses and reducing cholesterol efflux.[47] miRNAs also influence endothelial dysfunction, a key early event in atherosclerosis. miR-92a, enriched in endothelial cells exposed to disturbed flow, promotes endothelial activation and monocyte adhesion by targeting Krüppel-like Factor 2 (KLF2) and other atheroprotective genes. However, focusing solely on miR-92a may provide an incomplete understanding.[48] Other endothelial miRNAs play critical roles in early atherogenesis. For instance, miR-126, an endothelial-specific miRNA, is essential for maintaining vascular integrity and promoting reparative angiogenesis; its dysregulation is closely associated with endothelial dysfunction and atherosclerotic development.[49–51] Similarly, miR-103 has been implicated in modulating endothelial inflammation and permeability, further contributing to atherosclerosis.[52] Emerging evidence also points to miR-10a, which can suppress endothelial activation by inhibiting NF-κB signaling pathways, thereby reducing inflammatory responses. Moreover, the miR-221/222 cluster regulates endothelial nitric oxide synthase expression and vascular tone, underscoring its role in modulating endothelial function.[43] Collectively, these findings illustrate a multifaceted network of endothelial miRNAs that orchestrate vascular homeostasis and early atherogenic processes. This broader view emphasizes that a combination of miRNAs, rather than a single candidate, may better capture the complexity of endothelial regulation in atherosclerosis.

Immune crosstalk and risk factor amplification

CVD risk factors rarely act in isolation. The immune system plays a critical role in amplifying the effects of these risk factors through interconnected pathways. For example, obesity-induced inflammation exacerbates hypertension by promoting renal infiltration of immune cells, while diabetes-induced hyperglycemia accelerates atherosclerosis by enhancing monocyte activation and foam cell formation.[53] miRNAs serve as molecular mediators in these interactions, with dysregulated miRNA profiles observed across multiple risk factors. Circulating miRNA signatures have emerged as potential biomarkers for assessing cumulative CVD risk. For instance, elevated plasma levels of miR-122 and miR-126 have been linked to obesity-related dyslipidemia, while miR-21 and miR-155 correlate with hypertension and diabetes-induced vascular damage.[54] Targeting immune-mediated pathways using miRNA-based therapies offers promising strategies for mitigating CVD risk factors. For example, miRNA mimics and inhibitors, delivered via nanoparticles, are being explored to modulate inflammation, improve lipid metabolism, and restore endothelial function.[55] The development of miRNA-based biomarkers also holds potential for early detection and personalized management of individuals at high risk for CVD.[55]

Regulation of immune cells by miRNAs in the context of CVDs and related complications

The progression of CVDs is intrinsically linked to the dysregulation of immune cell function. Immune cells, including macrophages,

neutrophils, T lymphocytes, and regulatory Tregs, play critical roles in modulating inflammation, tissue remodeling, and repair. miRNAs have emerged as key regulators of these processes, influencing immune cell activation, polarization, and crosstalk. The intricate interplay between miRNAs and immune cells determines the balance between protective and pathological responses in CVDs such as myocardial infarction, atherosclerosis, and heart failure.[56]

Macrophage regulation by miRNAs in CVDs

Macrophages are central to the inflammatory response in CVDs, contributing to both tissue damage and repair. miRNAs regulate macrophage polarization into pro-inflammatory M1 or anti-inflammatory M2 phenotypes, influencing disease progression or resolution. miR-21, highly expressed in macrophages, plays a dual role in CVDs. It promotes M2 polarization by targeting the suppressor of cytokine signaling 1 (SOCS1), which enhances the production of anti-inflammatory cytokines such as interleukin-10.[57] This is particularly beneficial during the later stages of myocardial infarction when tissue repair and remodeling are critical. However, overexpression of miR-21 during the early inflammatory phase may exacerbate fibrosis and pathological remodeling by activating the TGF-β/mothers against decapentaplegic homolog (SMAD) signaling pathway.[58] miR-155, a hallmark of M1 macrophages, amplifies inflammation by targeting negative regulators of the NF-κB pathway, such as SHIP1 and SOCS1.[59] Elevated miR-155 levels have been associated with increased pro-inflammatory cytokine production and plaque destabilization in atherosclerosis, emphasizing its pathological role in advanced CVDs.[60] miR-223, predominantly expressed in myeloid cells, serves as a critical modulator of macrophage homeostasis. It suppresses excessive activation of inflammatory pathways by targeting transcription factors such as signal transducer and activator of transcription 3 and nuclear factor I-A, preventing chronic inflammation and foam cell formation in atherosclerosis.[61] Mice deficient in miR-223 exhibit aggravated inflammation and plaque instability, highlighting its protective role.[62]

Neutrophil regulation by miRNAs in acute and chronic inflammation

Neutrophils are the first responders to tissue injury, and their dysregulation can lead to excessive inflammation and tissue damage. miRNAs modulate neutrophil recruitment, activation, and lifespan in CVDs. miR-146a is a key regulator of neutrophilic inflammation, targeting IRAK1 and TRAF6 to suppress TLRs and NF-κB signaling pathways. Reduced miR-146a expression has been observed in patients with acute myocardial infarction, correlating with heightened neutrophil-driven inflammation.[63] Therapeutic restoration of miR-146a levels has been shown to mitigate neutrophil recruitment and improve outcomes in animal models of ischemic injury.[64] miR-223 also plays a role in neutrophil regulation, suppressing pro-inflammatory cytokine production and promoting neutrophil apoptosis. Dysregulation of miR-223 leads to prolonged neutrophil activation, exacerbating tissue damage during acute inflammation in myocardial infarction and chronic inflammation in heart failure.[65]

T lymphocyte regulation by miRNAs in CVDs

T lymphocytes, particularly $CD4^+$ subsets, significantly contribute to the immune landscape in CVDs. miRNAs regulate T cell activation, differentiation, and effector functions, influencing disease outcomes. miR-181a modulates TCR signaling thresholds, ensuring appropriate activation during immune responses. Age-related declines in miR-181a expression impair T cell activation, contributing to the immune senescence observed in elderly CVD patients.[66] Restoring miR-181a levels in preclinical models has shown promise in rejuvenating T cell function and improving immune responses.[67] The miR-17-92 cluster is crucial for the survival and proliferation of effector T cells. Dysregulation of this cluster impairs the generation of cytotoxic and memory T cells, weakening immune responses in chronic inflammation associated with heart failure and atherosclerosis.[68]

Regulatory T cells and miRNA regulation in CVDs

Tregs are essential for maintaining immune tolerance and preventing excessive inflammation (Fig. 4). miRNAs play a vital role in shaping Treg development, stability, and function. miR-142-3p and miR-142-5p regulate cyclic adenosine monophosphate signaling and TGF-β receptor expression, both of which are critical for Treg-mediated suppression of effector T cells. Dysregulation of these miRNAs impairs Treg function, exacerbating inflammatory responses in conditions like atherosclerosis and hypertension.[69] Although miR-155 is pro-inflammatory in macrophages, it plays a different role in Tregs, enhancing their proliferation and suppressive capacity by targeting the SOCS1 pathway. This dual function highlights the context-dependent nature of miRNA activity in immune regulation.[70]

The regulation of immune cells by miRNAs has profound implications for understanding and treating CVDs. miRNA-based therapies, including mimics and inhibitors, are being explored to restore immune balance. For example, nanoparticle-mediated delivery of miR-21 mimics has shown promise in enhancing macrophage-mediated tissue repair in myocardial infarction models.[32] Similarly, antagomiRs targeting miR-155 have demonstrated efficacy in reducing inflammation and plaque burden in atherosclerosis.[71] Circulating miRNAs also serve as potential biomarkers for monitoring immune cell activity in CVDs. Elevated plasma levels of miR-146a and miR-223, for instance, correlate with disease severity and outcomes in myocardial infarction and heart failure, offering minimally invasive tools for diagnosis and prognosis.[72] While these findings highlight the therapeutic potential of miRNA modulation, challenges such as off-target effects, delivery efficiency, and long-term safety must be addressed before clinical translation. Continued research into miRNAs' roles in immune cell regulation will pave the way for novel, targeted approaches to managing CVDs (Table 1).[73–87]

Recent research has highlighted the critical role of cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) in fine-tuning T cell responses, particularly in CVDs such as atherosclerosis and post-infarction cardiac remodeling.[88] Originally characterized for its role in immune tolerance and cancer immunotherapy, emerging data increasingly link CTLA-4 to vascular inflammation and myocardial injury.[88] Below is an updated overview of how CTLA-4 signaling, alongside relevant miRNA-mediated regulation, influences T cell biology and cardiovascular health.[89] T cell activation requires two main signals: (1) recognition of antigenic peptides presented on MHC class I or II molecules by the TCR and (2) co-stimulation via CD28 interaction with its ligands CD80 (B7-1) or CD86 (B7-2). Once activated, T cells initiate signaling cascades such as the phosphoinositide 3-kinases/Akt pathway, promoting proliferation, survival, and cytokine production. CTLA-4 competes with CD28 for binding to CD80/CD86, exerting an inhibitory effect that dampens T cell activation. When CTLA-4 is absent or blocked, T cells become hyperresponsive, potentially exacerbating inflammatory pathologies (Fig. 5).[90–92]

Preclinical studies underscore CTLA-4's importance in restraining pathological inflammation within the vascular endothe-

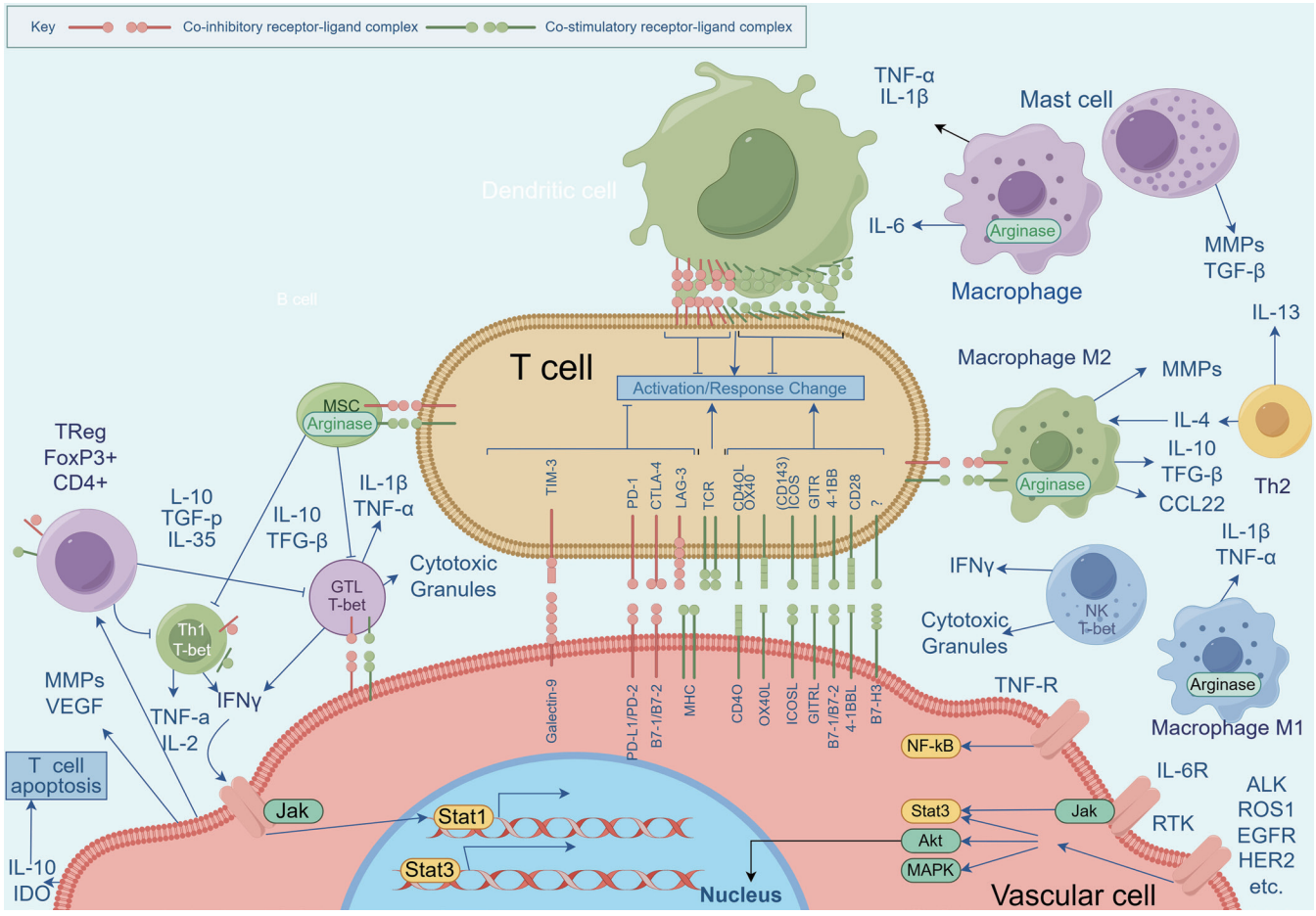

Fig. 4. Aspects of T cell recruitment by vascular cells may differ between species. Vascular cells, such as endothelial cells (ECs), modulate inflammation by regulating immune cell migration, activation status, and function. ALK, anaplastic lymphoma kinase; CCL22, C-C motif chemokine ligand 22; CD, cluster of differentiation; CTLA-4, cytotoxic T-lymphocyte associated protein 4; EGFR, epidermal growth factor receptor; GITR, glucocorticoid induced TNF receptor family-related protein; GITRL, glucocorticoid-induced TNF-related ligand; HER2, human epidermal growth factor receptor 2; ICOS, inducible T-cell costimulatory; IFNγ, interferon gamma; IL, interleukin; LAG-3, lymphocyte-activation gene 3; MAPK, mitogen-activated protein kinase; MHC, major histocompatibility complex; MMP, matrix metalloproteinase; MSC, mesenchymal stem cell; NF-kB, nuclear factor kappa-light-chain-enhancer of activated B cells; NK, natural killer; PD-1, programmed cell death 1; PD-L1, programmed death ligand 1; ROS, reactive oxygen species; RTK, receptor tyrosine kinase; TCR, T-cell receptor; TGF, transforming growth factor; Th1, type 1 T helper; TIM-3, hepatitis A virus cellular receptor 2; TNF, tumor necrosis factor.

lium. Mice deficient in CTLA-4 or treated with anti-CTLA-4 blocking antibodies exhibit larger atherosclerotic lesions, indicating that unchecked T cell activity accelerates plaque formation.[93] Conversely, overexpression of CTLA-4 or administration of abatacept (a CTLA-4 analog that competes with CD28 for CD80/CD86 binding) can reduce atherosclerotic lesion size, decrease T cell proliferation, and lower pro-inflammatory cytokine levels.[94] These findings suggest the therapeutic potential of CTLA-4 agonists or fusion proteins in mitigating arterial inflammation. In myocardial infarction models, CTLA-4 signaling has garnered attention. Hypoxia-induced stress on cardiomyocytes, particularly in post-infarction border zones, elevates the expression of costimulatory molecules like CD80/CD86, fueling an inflammatory environment. Administration of abatacept in this context has been shown to protect against excessive cardiac damage and improve survival in mouse models, aligning with observations in some patient cohorts where outcomes after MI are more favorable when T cell overactivation is restrained.[95,96]

Within the immune system, Tregs are a specialized subset that helps maintain self-tolerance and immune homeostasis. Tregs require the transcription factor forkhead box P3 (FOXP3) to retain their suppressive phenotype, and CTLA-4 is one of the key molecules driving their regulatory function.[97] By binding and depleting CD80/CD86 on antigen-presenting cells, Tregs limit costimulation to conventional T cells, reducing overall immune activation. This mechanism is especially relevant in pathologies where unchecked inflammation leads to tissue injury, such as advanced atherosclerosis and post-infarction remodeling. In recent years, attention has turned to miRNAs as crucial post-transcriptional regulators of CTLA-4 expression. Multiple miRNAs, including miR-9, miR-105, miR-155, and miR-487a-3p, directly target CTLA-4 transcripts, influencing T cell proliferation and effector functions.[89] Additional miRNAs, such as miR-24 and miR-210, can indirectly suppress CTLA-4 by downregulating FOXP3, thereby impacting Treg stability and immunosuppressive capacity.[89] Among these, miR-155 has garnered particular attention. Studies in cancer and inflammatory models suggest that miR-155 can reduce CTLA-4 levels by binding to the 3′UTR of its mRNA in both Treg and con-

Table 1. MicroRNAs and their key targets in modulating regulatory T cell (Treg) function

miRNA	Regulation	Targets	Biological effects	Reference
miR-155-5p	Down	SOCS1	FOXP3 induces the expression of miR-155-5p in Tregs. Deficiency in miR-155 disrupts STAT5 signaling, leading to a decrease in Treg numbers and imbalance in immune regulation	73
miR-142-3p	Down	TGFBR1, TET2, KDM6A	Reduced levels of miR-142-3p enhance FOXP3 expression and suppressive Treg activity by increasing KDM6A and BCL-2 levels through the demethylation of H3K27me3. It also boosts TGFBR1 expression, helping prevent the rejection of mismatched allografts	74–76
miR-340-5p	Down	IL-4	In allergic rhinitis, increased expression of miR-340-5p hinders the formation and functionality of Tregs, contributing to impaired immune tolerance	77
miR-125a-5p	Down	STAT3, IFNG, IL-13	The absence of miR-125a-5p reduces Treg populations, worsening conditions like colitis and experimental autoimmune encephalomyelitis (EAE) by promoting inflammatory responses. This miRNA plays a crucial role in maintaining the stability and balance of Tregs	78
miR-4281-3p	Up	FOXP3	Through interaction with the TATA-box in the FOXP3 promoter, miR-4281-3p enhances FOXP3 expression, improving Treg differentiation, functionality, and persistence	79
miR-202-5p	Up	MATN2	Elevated miR-202-5p levels in allergic rhinitis negatively affect the development and suppressive capabilities of Tregs, leading to reduced immune regulation	80
miR-15a-5p/16-5p	Up	FOXP3	Overexpression of miR-15a-5p/16-5p reduces FOXP3 levels, impairing the suppressive capabilities of Tregs and potentially affecting immune tolerance	81
miR-146a-5p	Down	STAT1	The lack of miR-146a-5p in Tregs leads to a failure in tolerogenic mechanisms and promotes a shift toward Th1 immune responses, disrupting immune balance	82
miR-181a/b-5p	Down	CTLA-4	Deficiency in miR-181a/b-5p affects thymic Treg formation but enhances the suppressive activity of peripheral Tregs, contributing to a complex regulatory balance	83
miR-24-3p	Down	FOXP3	Although naturally low in Tregs, artificial overexpression of miR-24-3p decreases FOXP3 expression, impairing Treg function and stability	84
miR-1224-5p	Down	FOXP3	AhR signaling suppresses miR-1224-5p, leading to increased FOXP3 expression and Treg maturation, helping mitigate systemic inflammation caused by pertussis toxin	85
miR-146b-5p	Down	TRAF6	Using antagomirs to reduce miR-146b-5p expression enhances thymic Treg effectiveness and their inhibitory impact on graft-versus-host disease (GvHD)	86
miR-142-5p	Down	PDE3B	The suppression of miR-142-5p in Tregs reduces cAMP levels, impairing Treg activation and peripheral tolerance. This results in systemic autoimmune inflammation	87

BCL-2, BCL2 apoptosis regulator; cAMP, chromosome alignment maintaining phosphoprotein 1; CTLA-4, cytotoxic T-lymphocyte associated protein 4; FOXP3, forkhead box P3; IFNG, interferon gamma; IL, interleukin; KDM6A, lysine demethylase 6A; MATN2, matrilin 2; PDE3B, phosphodiesterase 3B; SOCS1, suppressor of cytokine signaling 1; TATA, TATA containing gene; TET2, Tet methylcytosine dioxygenase 2; TGFBR1, transforming growth factor beta receptor 1; TRAF6, TNF receptor associated factor 6.

ventional T cells, lowering the activation threshold for T cells.[98] However, recent findings indicate that miR-155 may require cooperation with other RNA-binding proteins or miRNAs to achieve full repression of CTLA-4 (Fig. 6).[99,100] This interplay likely varies in different disease contexts, such as myocardial ischemia and atherosclerosis, where cytokine milieus and hypoxic signals modulate miRNA expression. Building on these insights, novel therapeutic strategies are exploring ways to modulate CTLA-4 and its regulatory miRNAs to achieve better outcomes in CVDs. Agents like abatacept reduce detrimental inflammation by blocking costimulatory signals, thus protecting arterial walls and the ischemic myocardium. Targeting miR-155 or other miRNAs that downregulate CTLA-4 could be a future approach to reinforce Treg function. However, off-target effects remain a concern, and additional cofactors may be needed for a robust clinical response. Combining CTLA-4–focused immunotherapy with established cardiovascular interventions (e.g., lipid-lowering agents, anti-hypertensives) may yield synergistic benefits, particularly for patients with high inflammatory burdens post-MI or advanced atherosclerosis.

Despite these promising leads, further investigation is essential to clarify how miRNAs, RNA-binding proteins, and inflammatory mediators orchestrate CTLA-4 expression *in vivo*. Mapping these regulatory networks can guide the development of next-generation immunomodulatory treatments that preserve the delicate balance between pro- and anti-inflammatory pathways in CVD. Understanding the underlying molecular details will also facilitate personalized strategies, ensuring that interventions targeting CTLA-4 and associated miRNAs are both effective and safe for diverse patient populations. In summary, recent evidence underscores CTLA-4's pivotal role in regulating T cell activation and preventing excessive immune damage in cardiovascular settings. Ongoing exploration of CTLA-4 and its post-transcriptional control by miRNAs promises to expand our therapeutic toolkit, offering new hope for individuals with advanced atherosclerosis and ischemic heart disease (Table 2).[62,101–112]

Future directions and limitations

The growing body of evidence surrounding miRNA-based interventions in CVDs underscores both the promise of these therapies

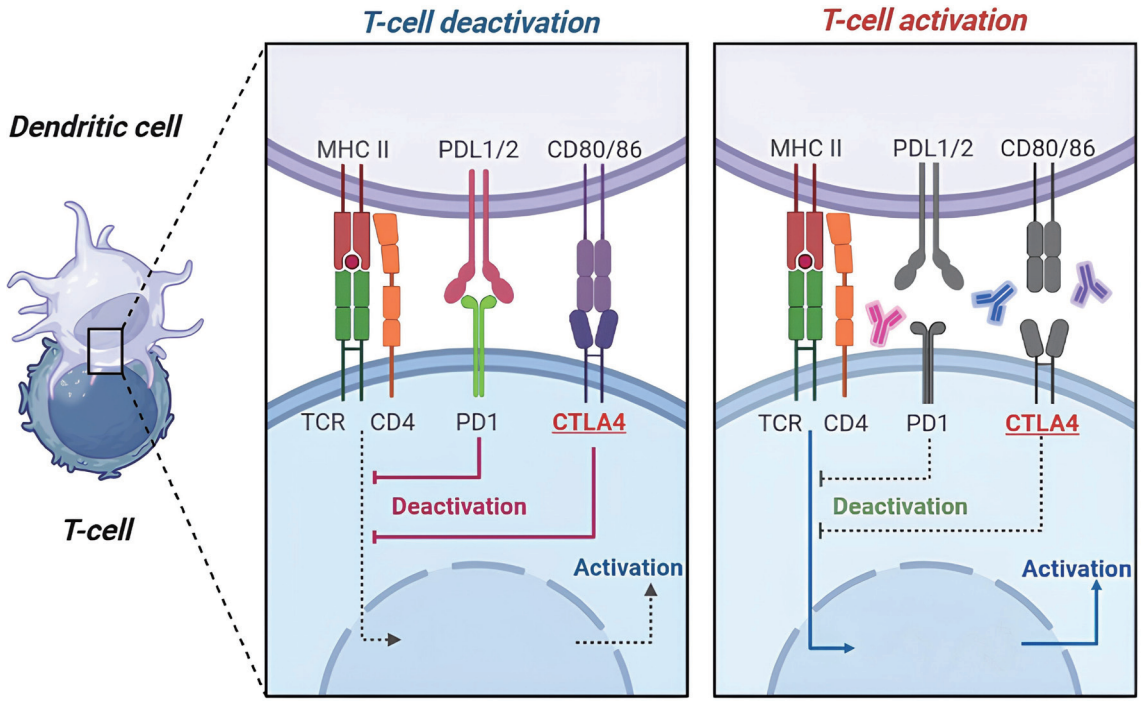

Fig. 5. Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) in regulatory T cells (Tregs) and dendritic cells. CD, cluster of differentiation; MHC, major histocompatibility complex; PD1, programmed cell death 1; PDL1, programmed death ligand 1; TCR, T-cell receptor.

and the formidable challenges ahead. Recent preclinical and early clinical findings highlight the potential of manipulating specific miRNAs to curb pathological processes such as chronic inflammation, fibrosis, and endothelial dysfunction. However, translating these insights into robust, safe, and effective clinical interventions will require systematic refinement of current strategies, innovative delivery methods, and integration of knowledge from immunology, materials science, and regulatory biology.

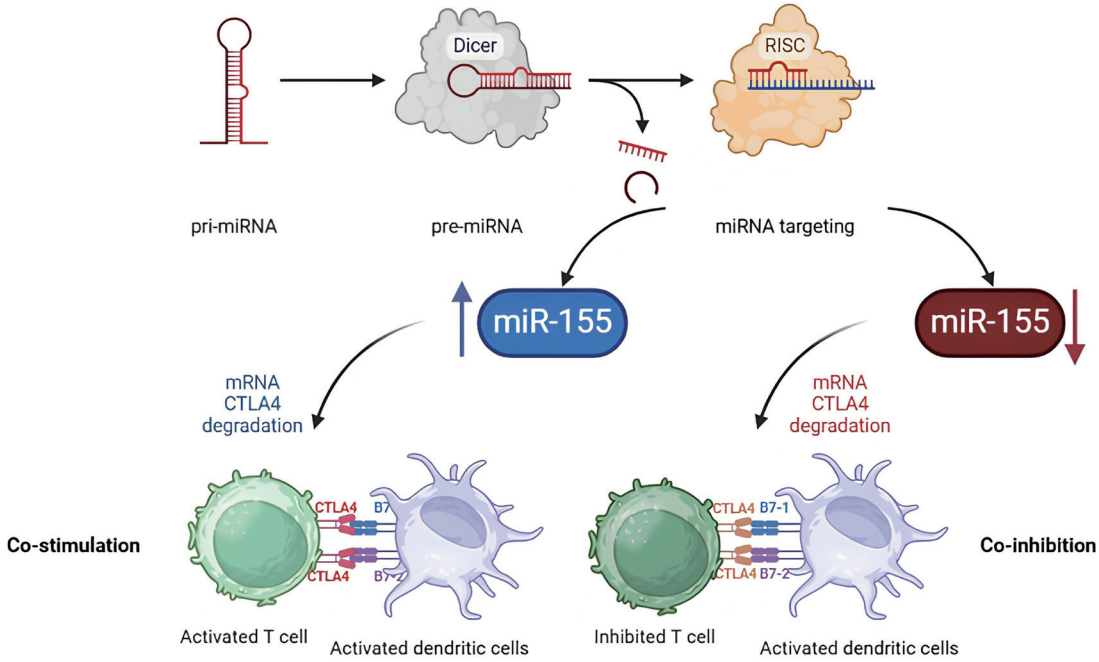

Fig. 6. Post-transcriptional silencing of cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) by miR-155 in Treg cells may contribute to reducing CTLA-4 mRNA expression observed in cardiovascular diseases. Overall, miR-155 can activate CTLA-4 in T cells, suggesting a role for miR-155 as a temporal filter regulating the onset of inflammation by activating CTLA-4 expression. miRNA, microRNA; mRNA, messenger RNA; RISC, RNA-induced silencing complex.

Table 2. Summary of key immune-derived miRNAs in cardiovascular diseases: mechanisms, functions, and therapeutic implications

miRNAs	Key findings	Impact/Applications	Mechanism of action	Functions	Reference
miR-21, miR-155, and miR-146a	Explores how immune-miRs regulate gene expression in immune cells and their contribution to cardiovascular disease progression	Highlights their potential as biomarkers for early diagnosis and disease progression	miR-21 targets PTEN, activating the PI3K/Akt pathway, promoting cell survival	Inflammatory response regulation, vascular remodeling, apoptosis inhibition	101
miR-146a, miR-155, and miR-223	Investigates the role of immune-miRs in modulating immune signaling pathways affecting innate and adaptive immune responses in CVD	Suggests potential therapeutic targets for treating inflammation and CVD	miR-146a inhibits NF-κB signaling by targeting TRAF6 and IRAK1	Modulates inflammation, immune cell function, fibrosis in vascular tissues	102
miR-146a and miR-155	Discusses the role of inflamma-miRs in regulating inflammation in cardiovascular disease and their association with atherogenesis.	Offers insights into using inflamma-miRs as biomarkers for atherosclerosis and CVD	miR-155 enhances macrophage activation via JAK/STAT pathway	Promotes atherosclerosis, endothelial dysfunction, macrophage polarization	103
miR-1, miR-133a, and miR-21	Focuses on specific miRNAs as diagnostic biomarkers for heart failure and their expression profiles in patients	Demonstrates the feasibility of using miRNAs as biomarkers for heart failure diagnosis	miR-1 and miR-133a target GATA4 and Hand2, influencing cardiac development	Cardiac muscle function regulation, response to stress, cell differentiation	104
miR-21 and miR-155	Reviews the involvement of miRNAs in immune activation and inflammation during heart failure, emphasizing their therapeutic potential	Suggests miRNAs as targets for modulating immune responses in heart failure treatment	miR-21 promotes fibrosis by targeting SMAD7 and TGF-β signaling pathway	Fibrosis regulation, cardiac remodeling, inflammation in myocardial infarction	105
miR-155	Highlights miR-155's involvement in cardiovascular inflammation, especially in atherosclerosis, and its potential as a therapeutic target	Focuses on miR-155 as a crucial mediator in inflammatory pathways in CVD	miR-155 targets SOCS1, enhancing inflammation by promoting NF-κB activation	Pro-inflammatory response, vascular injury, endothelial cell dysfunction	106
miR-223	miR-223 is involved in myeloid cell differentiation and modulation of immune responses, influencing atherosclerosis progression	Suggests miR-223 as a therapeutic target for modulating inflammation in CVD	miR-223 targets NFI-A and regulates granulocyte differentiation and inflammatory response	Myeloid differentiation, immune cell modulation, suppression of inflammation	62
miR-146a	Examines miR-146a's role in modulating inflammation by targeting key inflammatory pathways in CVD, such as the TLR and NF-κB pathways	Proposes miR-146a as a potential therapeutic target for controlling inflammation in CVD	miR-146a inhibits TLR/IL-1R signaling by targeting IRAK1 and TRAF6	Anti-inflammatory function, modulation of immune response, vascular health	107
miR-21	Reviews the dual role of miR-21 in promoting fibrosis and inflammation during myocardial infarction and heart failure	Identifies miR-21 as a biomarker for fibrosis and as a therapeutic target in CVD	miR-21 activates the PI3K/Akt pathway by inhibiting PTEN, promoting fibrosis	Fibrosis promotion, tissue remodeling, anti-apoptotic function.	108
miR-223	Explores how exosomal miR-223 can modulate inflammatory responses and prevent endothelial damage, highlighting its role as a non-invasive biomarker	Suggests the potential of exosomal miR-223 in therapeutic strategies for CVD	miR-223 is secreted via exosomes and regulates endothelial function by targeting NF-κB	Modulation of endothelial function, immune cell response, reduction of vascular damage	109
miR-92a and miR-126	Investigates the role of miRNAs in regulating endothelial function and promoting inflammation in atherosclerosis	Identifies miR-92a and miR-126 as key regulators of vascular inflammation in CVD	miR-92a regulates endothelial cell junctions and angiogenesis via integrins	Endothelial barrier function, inflammatory responses in atherosclerosis	110
miR-21 and miR-92a	Focuses on circulating miRNAs that serve as biomarkers for early detection and prognosis in acute myocardial infarction	Highlights the use of circulating miRNAs in early diagnosis of myocardial infarction	miR-21 and miR-92a are released from injured myocardial cells, influencing inflammation	Cardiovascular injury markers, inflammation resolution, early diagnosis	111
miR-34a	Reviews the involvement of miR-34a in endothelial aging and its contribution to cardiovascular diseases such as hypertension and atherosclerosis	Discusses the potential of miR-34a as a target for anti-aging therapies in CVD	miR-34a inhibits SIRT1, leading to increased cellular senescence and aging	Endothelial aging, cellular senescence, inflammation regulation	112

Akt, serine/threonine kinase 1; CVD, cardiovascular disease; IL, interleukin; IRAK1, interleukin 1 receptor associated kinase 1; JAK, Janus kinase; miRNAs, microRNAs; NFI-A, nuclear factor I-A; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; PI3K, phosphatidylinositol 3-kinase; PTEN, phosphatase and tensin homolog; SIRT1, sirtuin 1; SOCS1, suppressor of cytokine signaling 1; STAT, sterol O-acyltransferase 1; TGF-β, transforming growth factor beta; TLR, Toll like receptors; TRAF6, TNF receptor associated factor 6.

A key milestone in miRNA therapeutics has been the transition from preclinical studies to initial clinical investigations. Two early clinical reports evaluated the safety and preliminary efficacy of miRNA modulation in patients with heart failure.[113,114] These trials demonstrated encouraging safety profiles for miRNA modulators, providing a foundation for larger, multicenter trials that will be critical for defining optimal dosing regimens, long-term effectiveness, and potential off-target effects. Such studies should include detailed patient stratification—using biomarkers, comorbidities, and genetic background—to identify which subgroups derive the greatest benefit from miRNA therapies. Overcoming barriers such as variable miRNA expression across patient populations and disease stages will likely require multiparametric analyses that account for environmental factors such as diet and exercise that influence cardiovascular risk.

One of the most pressing challenges in miRNA-based therapy is achieving precise and efficient delivery to disease-relevant tissues and cell types. Recent work has demonstrated the potential of nanoparticle-mediated delivery systems for miR-21 inhibitors in post-myocardial infarction models, showcasing improvements in cardiac function through the reduction of pathological remodeling.[115] However, this and other preclinical approaches rely on carefully engineered platforms—such as biodegradable polymers, liposomes, or viral vectors—that must meet various criteria, including biocompatibility, immunogenicity, stability in circulation, and tissue specificity. Moving forward, advances in nanotechnology and polymer science will likely enhance targeted delivery. Cell-specific targeting ligands, for instance, could direct miRNA mimics or inhibitors to pathological immune cell subsets infiltrating atherosclerotic plaques or infarcted myocardium, reducing systemic exposure and off-target effects—critical considerations given that miRNAs regulate many biological pathways.[95,96] Innovative exosome engineering is another promising direction, leveraging the inherent biocompatibility of these naturally occurring vesicles and their ability to deliver cargo to specific cell types. This approach could help mitigate immune responses triggered by artificially manufactured carriers.

Chronic inflammation is central to atherogenesis, plaque instability, and adverse cardiac remodeling. Multiple studies have illustrated how miRNAs modulate chemokine and chemokine receptor expression, influencing immune cell trafficking and activation in CVDs.[116–119] By fine-tuning these chemokine axes, miRNA-based strategies could offer unprecedented control over immune cell recruitment, potentially stabilizing plaques and reducing inflammatory burden without globally suppressing the immune system. Future studies must explore the best ways to harness this knowledge. For instance, miR-155 antagomiRs can dampen pro-inflammatory macrophage activity, but this same miRNA can also have protective roles in certain immune contexts. Likewise, modulating miRNAs that target chemokine receptors must account for feedback loops, such as compensatory upregulation of other inflammatory pathways. Detailed mapping of miRNA-chemokine networks at the cellular and tissue level will be crucial for optimizing therapeutic regimens that safely achieve immune homeostasis.

While conventional approaches rely on miRNA mimics or antagomiRs to alter miRNA levels, clustered regularly interspaced short palindromic repeats (CRISPR)-based technologies have opened the door to more permanent and precise modifications.[83] CRISPR/Cas tools can directly edit miRNA genes or their regulatory sequences, potentially correcting dysregulated miRNAs implicated in CVDs. Nevertheless, issues such as efficiency, mosaicism, and off-target editing must be addressed before gene editing becomes a clinically viable strategy. Simultaneously, artificial intelligence (AI)-driven methods are playing an increasingly important role in CVD research. By integrating large-scale multi-omics data—encompassing genomics, proteomics, metabolomics, and transcriptomics—AI can identify robust miRNA signatures that correlate with disease progression or therapeutic response. These computational models could guide personalized treatment strategies, predicting which miRNA targets would have the highest likelihood of success in specific patient subpopulations. Moreover, AI could refine delivery approaches by modeling the interactions of various carrier systems within the complex cardiovascular environment. Current single cell sequencing platforms are not optimized to detect mature miRNAs, which limits the ability to directly measure miRNA expression in individual cells.[52] However, new specialized protocols and indirect inference methods are emerging, allowing researchers to correlate single-cell gene expression profiles with known miRNA-target interactions. Improvements in sample preparation and library construction may soon allow precise identification of miRNA roles in distinct immune cell subsets (e.g., M1 vs. M2 macrophages, T effector vs. T regulatory cells) within an atherosclerotic lesion or infarct area.

An intriguing frontier in CVD research is the interplay between the gut microbiome and miRNA expression. Early evidence suggests that microbiota composition influences systemic inflammation and immune cell phenotypes by altering the expression of regulatory miRNAs, such as miR-146a and miR-155.[85] Future studies could explore whether modulating the gut microbiome—through diet, probiotics, or antibiotics—synergizes with miRNA-based therapies to yield superior cardiovascular outcomes. This dual-target approach could be especially beneficial for individuals whose microbiome profile contributes to a heightened inflammatory state.

Finally, drawing parallels with more advanced fields like cancer immunotherapy could further accelerate progress. In oncology, miRNAs have been used to enhance immune checkpoint inhibition and fine-tune T cell activity. A similar strategy could be adapted for CVDs, where immune checkpoints like CTLA-4 mediate vascular inflammation and plaque development. Identifying miRNAs that regulate these pathways in T cells could lead to combination therapies that pair miRNA modulators with traditional or experimental immunomodulatory agents, offering personalized treatment regimens that target pathological immune activation without compromising systemic immune competence.

In summary, research over the past decade has firmly established miRNAs as pivotal regulators of immune-driven cardiovascular pathologies. Early clinical trials have begun to address the feasibility and preliminary safety of miRNA-based therapies, laying the groundwork for more comprehensive investigations.[113,114] However, critical questions remain regarding optimal delivery systems, off-target risks, tissue-specific expression, and the long-term sustainability of miRNA interventions. As more refined technologies—from CRISPR/Cas gene editing to AI-driven biomarker discovery—converge with an evolving understanding of chemokine networks and gut microbiome interactions, the field stands on the brink of transformative breakthroughs. Addressing current limitations and rigorously validating novel approaches will ultimately determine whether miRNAs can fulfill their potential as cornerstone therapies in personalized cardiovascular medicine (Table 3).[8,17,18,21,49–52,59,61,62,98–100,106,107,109,120–127]

Conclusions

Immune-derived miRNAs have emerged as critical regulators in

Table 3. Immune-derived miRNAs (immuno-miRs) as diagnostic and therapeutic tools in CVDs

miRNA	Primary cellular source/context	Role in CVD pathogenesis	Diagnostic/Prognostic utility	Therapeutic potential	Reference
miR-21	Macrophages, cardiac fibroblasts; also secreted in extracellular vesicles	Modulates inflammation, fibrosis, and tissue remodeling; dual role in early (pro-inflammatory) and later (repair) phases	Elevated plasma levels correlate with adverse outcomes in myocardial infarction (MI) and heart failure; potential biomarker for fibrosis	Inhibitors (antagomiRs) may reduce pathological remodeling and fibrosis	120–122
miR-146a	Innate immune cells (e.g., neutrophils, macrophages)	Acts as a negative regulator of inflammation by targeting IRAK1 and TRAF6; modulates Toll-like receptor signaling	Lower or dysregulated levels associated with exacerbated inflammation in atherosclerosis and heart failure; candidate for risk stratification	miRNA mimics could restore regulatory functions to suppress excessive inflammation	21,52,59,107
miR-223	Myeloid cells (macrophages and neutrophils)	Regulates macrophage polarization and limits excessive inflammatory activation; contributes to plaque stability	Circulating levels reflect immune cell activation and plaque composition in atherosclerosis; potential prognostic marker	miR-223 mimics might be used to balance macrophage responses and stabilize plaques	8,17,18,61,62,109
miR-155	Expressed in both macrophages and neutrophils (and other immune cells)	Promotes pro-inflammatory responses via NF-κB signaling; involved in atherogenesis and myocardial injury; context-dependent roles (can be anti-inflammatory in certain stages)	Elevated in inflammatory conditions such as atherosclerosis and MI; useful in evaluating immune activation status	AntagomiRs targeting miR-155 may reduce excessive inflammation and improve outcomes	98–100,106
miR-122	Although primarily liver-derived, its circulating levels reflect systemic lipid metabolism	Contributes to dyslipidemia and atherosclerosis through regulation of cholesterol and lipid homeostasis	Serves as a biomarker for lipid dysregulation and associated atherosclerotic risk	Inhibiting miR-122 may improve cholesterol efflux and reduce plaque formation	123
miR-126	Endothelial cells (EC-specific)	Critical for maintaining endothelial integrity, angiogenesis, and vascular homeostasis; influences endothelial activation in atherosclerosis	Altered levels are associated with endothelial dysfunction and vascular injury; potential marker for early CVD detection	miR-126 mimics could enhance endothelial repair and promote vascular health	49–51
miR-33	Lesional macrophages and liver (species-specific: miR-33a in mice; miR-33a/b in humans/primates)	Regulates cholesterol efflux by targeting ATP-binding cassette transporters (e.g., ABCA1); contributes to foam cell formation and atherosclerotic plaque progression	Circulating levels may reflect lipid metabolism disturbances and atherosclerotic burden	Inhibitors of miR-33 can enhance cholesterol efflux and reduce foam cell formation	124–127

CVD, Cardiovascular disease; IRAK1, interleukin 1 receptor associated kinase 1; miRNA, microRNAs; TRAF6, TNF receptor associated factor 6.

CVDs, influencing both innate and adaptive immune responses. Our review demonstrates that specific miRNAs—such as miR-21, miR-146a, miR-223, miR-122, miR-126, and miR-155—play pivotal roles in mediating inflammation, modulating tissue repair, and maintaining immune homeostasis. Their ability to circulate within extracellular vesicles highlights their potential as minimally invasive biomarkers for early diagnosis, risk stratification, and monitoring disease progression in conditions such as myocardial infarction, atherosclerosis, and heart failure. Moreover, preclinical studies on miRNA-based therapeutics, using mimics and inhibitors, indicate promising strategies for targeting dysregulated immune responses in CVDs. These approaches, by directly modulating specific miRNAs, have shown potential to reduce pathological inflammation and promote tissue repair. However, challenges remain in translating these findings into clinical practice. Issues such as the complexity of miRNA regulatory networks, potential off-target effects, and difficulties in achieving efficient, cell-specific delivery must be carefully addressed. Overall, the evidence supports the transformative potential of immune-derived miRNAs as diagnostic, prognostic, and therapeutic tools in cardiovascular medicine. Future research should focus on refining these strategies through advanced technologies, including high-throughput sequencing, gene editing, and artificial intelligence. Overcoming current translation barriers will be crucial for unlocking the full potential of immune-derived miRNAs, paving the way for more personalized and effec-

tive cardiovascular care, ultimately improving patient outcomes and reducing the global burden of CVDs.

Acknowledgments

The authors utilized the highly esteemed software BioRender and FigDraw 2.0. to create the figures for this manuscript. BioRender.com (2025) and FigDraw (2025). Retrieved from https://www.biorender.com and https://www.figdraw.com.

Funding

This work was supported by the Bashkir State Medical University Strategic Academic Leadership Program (PRIORITY-2030).

Conflict of interest

IG has been an editorial board member of *Gene Expression* since February 2025. The authors have no other conflict of interest to note.

Author contributions

Conceptualization, writing—original draft preparation, writing—review and editing (IG, OB), validation, investigation, resources, and visualization (VP, LG, AS, HS), project administration, and funding acquisition (IG). All authors have read and agreed to the published version of the manuscript.

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