# Decoding miRNA-146a: Mechanisms of action in cardiovascular diseases and endocrine metabolic disorders (Review)

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**Abstract.** MicroRNA-146a (miR-146a) has emerged as a core regulatory molecule in inflammation and metabolism in recent years, and the present review systematically elucidates its critical role and regulatory mechanisms in cardiovascular diseases as well as endocrine and metabolic disorders. Evidence indicates that miR-146a negatively regulates the nuclear factor-κB inflammatory signaling pathway by targeting key molecules such as tumor necrosis factor receptor-associated factor 6 and interleukin-1 receptor-associated kinase 1. This regulation impacts various pathophysiological processes, including immune response, inflammatory reactions, oxidative stress, cell apoptosis and proliferation, autophagy, and anti-fibrosis. The molecule demonstrates a bidirectional dynamic regulatory feature, exhibiting either protective or maladaptive effects in different diseases and stages of disease, particularly in the progression of cardiovascular conditions (such as myocardial ischemia-reperfusion injury and atherosclerosis) and endocrine and metabolic disorders (such as diabetes and its complications). Additionally, miR-146a serves as a significant biomarker and therapeutic target. Future research should focus on further elucidating its cell- and disease course-specific mechanisms while promoting the clinical translation of therapeutic strategies based on targeted delivery systems.

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*Abbreviations:* ceRNA, competitive endogenous RNA; CLP, cecal ligation and puncture; DPN, diabetic peripheral neuropathy; EGFR, epidermal growth factor receptor; EndMT, endothelial-to-mesenchymal transition; FGF2, fibroblast growth factor 2; HAECs, human aortic endothelial cells; HUVECs, human umbilical vein endothelial cells; ICAM-1, intercellular adhesion molecule 1; I/R, ischemia/reperfusion; lncRNA, long non-coding RNA; IRAK1, interleukin-1 receptor-associated kinase 1; JNK, c-Jun N-terminal kinase; LPS, lipopolysaccharide; MED1, mediator complex subunit 1; MDA, malondialdehyde; MIRI, myocardial ischemia-reperfusion injury; MLNP, mannose-modified lipid nanoparticles; miRNA, microRNA; MSC, mesenchymal stem cell; NOX4, NADPH oxidase 4; NF-κB, nuclear factor κ-light-chain-enhancer of activated B cells; NCV, nerve conduction velocity; PIC, polyion complex; PLGA, poly(lactic-co-glycolic acid); ROS, reactive oxygen species; SIC, sepsis-induced cardiomyopathy; SOD, superoxide dismutase; SOX2-OT, SOX2 overlapping transcript; STAT, signal transducer and activator of transcription; STEMI, ST-segment elevation myocardial infarction; TGF, transforming growth factor; TLR, Toll-like receptor; T2DM, type 2 diabetes; TRAF6, TNF receptor-associated factor 6; TXNIP, thioredoxin-interacting protein; VCAM-1, vascular cell adhesion molecule 1; 3' UTR, 3' untranslated region

*Key words:* microRNA-146a, cardiovascular diseases, endocrine metabolic disorders, molecular mechanism, delivery system

## Contents



## 1. Introduction

MicroRNAs (miRNAs or miRs) are a class of small non-coding RNA molecules comprising 20-25 nucleotides. This type of molecule has a unique function. It can inactivate specific mRNA while interfering with the translation of target proteins, thereby regulating the expression of other genes (1,2). A previous study has suggested that the mRNAs transcribed from ~60% of human genes can be bound by miRNAs (3). However, the latest research has constructed an experimentally validated miRNA-mRNA interaction network by integrating multi-source high-confidence datasets. Notably, only approximately one-fifth of human genes have verified regulatory

interactions with miRNAs (4). In cell activities, miRNAs play indispensable roles in key developmental processes, such as cell proliferation, apoptosis, and differentiation (5,6). Located on chromosome 5, miR-146a is a member of the miRNA family and has unique characteristics and functions within the miRNA family (7). Reportedly, miR-146a has various biological functions (8-10). Its wide targets significantly affect the organism and extensively participate in a series of key bioprocesses including immune regulation (8), inflammatory response (9), oxidative stress (10), apoptosis and proliferation (11), autophagy (12), anti-fibrosis (13), anti-convulsant (14), analgesia (15), and antitumor (16).

Experimentally, miR-146a is closely related to the occurrence and development of diverse diseases, which involve multiple systems, encompassing cardiovascular diseases (17-19) and endocrine and metabolic diseases (20). Its mechanism of action involves multiple levels of detailed regulation. Currently, miR-146a has been widely regarded by the scientific research community as a potentially valuable biomarker and a promising therapeutic target for various diseases (21-23). In the present review, the production process, fine regulatory mechanism and diverse functions of miR-146a are explicitly introduced. Concurrently, the latest research progress on the molecular mechanisms of miR-146a in the development of various systemic diseases, as well as a series of therapeutic strategies based on miR-146a, are systematically summarized. The present review is expected to provide novel insights and solid theoretical basis for diagnosis, treatment and prognosis assessment of related diseases, along with the development of efficient targeted intervention utilizing miR-146a as the core.

## 2. Generation and regulation of miR-146a

*Generation of miR-146a*. In 2002, Lagos-Quintana *et al* (24) successfully identified the presence of miR-146 among mouse heart tissues for the first time through experimental research. In 2006, Taganov *et al* (25) further conducted research on humans and clarified the gene location and regulatory mechanism of the miR-146 family. This directly confirmed that members of this family also existed in the human body (25). As core members of the miR-146 family, miR-146a and miR-146b are positioned in the q33 region of chromosome 5 and the q24 region of chromosome 10, respectively (26). Notably, their functions are highly similar (26,27).

As illustrated in Fig. 1, miR-146a is transcribed by RNA polymerase II into the long primary transcript pri-miR-146a. Subsequently, miR-146a is cleaved by the nuclear Drosha-DiGeorge syndrome critical region 8 (DGCR8) complex to generate pre-miR-146a, which is subsequently transported to the cytoplasm through the exportin-5/Ras-related nuclear protein guanosine triphosphate pathway (28-30). After being processed by the Dicer-TAR RNA binding protein (TRBP) complex to produce mature double-stranded miRNA, miR-146a is assembled into the RNA-induced silencing complex (RISC) and exerts post-transcriptional inhibitory effects by targeting the 3' UTR of target mRNAs (31,32). Both arms of this precursor can generate two mature isoforms, miR-146a-5p and miR-146a-3p. Notably, the former possesses higher biological activity (26).

*Regulation of miR-146a*. The regulation of miR-146a expression is an intricate network involving multiple levels and molecules. Reportedly, the expression of miR-146a is mainly regulated by epigenetic modifications, transcription factor regulation, upstream non-coding RNA [such as long non-coding RNA (lncRNA) and circular RNA (circRNA)] intervention, and multiple signaling pathways (Fig. 2) (33-37). Its physiological expression is key to homeostasis, while pathological dysregulation drives the progression of various diseases.

*Epigenetic modification regulation*. Epigenetic modification represents a significant mechanism for regulating the expression of miR-146a. One study has confirmed that histone H3 lysine 27 trimethylation (H3K27me3), catalyzed by the histone methyltransferase enhancer of zeste homolog 2, is specifically enriched in the promoter region of miR-146a-5p, thereby inhibiting its transcription (33).

*Transcription factors and signaling pathway regulation*. Nulcear factor κ-light-chain-enhancer of activated B cells (NF-κB) functions as the core transcriptional activator of miR-146a; under inflammatory stimuli such as interleukin (IL)-1β, lipopolysaccharide (LPS), and tumor necrosis factor (TNF)-α, NF-κB is activated and binds to the promoter region of miR-146a, inducing its transcription (25). Additionally, IFN-γ has been reported to upregulate miR-146a expression further by activating the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) signaling pathway, contributing to the regulation of the inflammatory response in autoimmune diseases (34). Oxidized low-density lipoprotein (oxLDL) has been shown to upregulate miR-146a through the c-Jun N-terminal kinase (JNK) and NF-κB signaling pathways (35).

*Upstream non-coding RNA regulation*. In the competitive endogenous RNA (ceRNA) network, various upstream non-coding RNAs have been shown to negatively regulate the function of miR-146a via the 'molecular sponge' effect. For example, lncRNA CHRF was found to exacerbate IL-6-induced inflammatory damage in ATDC5 cells by downregulating miR-146a (36). LncRNA CRNDE and lncRNA HCG18 were demonstrated to function as molecular sponges that adsorb miR-146a-5p, competitively inhibiting its binding to downstream target genes and thereby suppressing its function (38,39). In addition to lncRNAs, circRNAs also play pivotal roles in the regulation of miR-146a. Studies have identified circRNA ATF6, circRNA Fbxl5, and circRNA RASGEF1B as negative regulators of miR-146a expression through their ability to sequester miR-146a, subsequently decreasing its inhibitory or promoting effects on downstream target genes (40-42).

*Regulation related to disease states*. The expression levels of miR-146a display significant variability across different disease states, often closely associated with the pathological characteristics of each condition. In the context of diabetes, persistently elevated pro-inflammatory cytokines, such as TNF-α and IL-6, in conjunction with excessive accumulation of reactive oxygen species (ROS), disrupt the normal transcriptional and post-transcriptional processing of miR-146a. This disruption undermines the homeostatic negative feedback regulation on the Toll-like

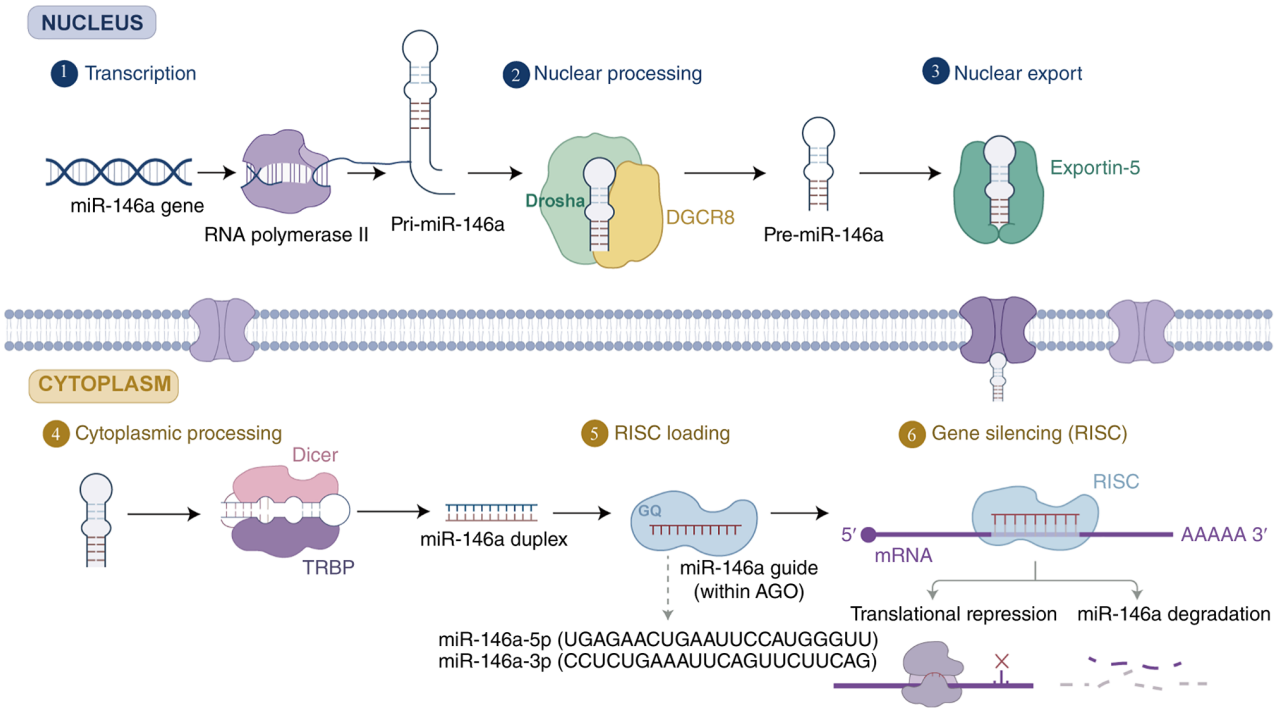


Figure 1. Biogenesis of miR-146a.miR-146a is transcribed by RNA polymerase II into the primary transcript pri-miR-146a, which is processed by the nuclear Drosha-DGCR8 complex into the precursor pre-miR-146a and then transported to the cytoplasm. There, it is cleaved by the Dicer-TRBP complex to generate mature miR-146a, which is finally assembled into the RISC complex to achieve post-transcriptional gene silencing by targeting the 3' UTR of target mRNAs. miR-146a, microRNA-146a; pri-miR, primary miRNA transcript; DGCR8, DiGeorge syndrome critical region 8; Dicer, RNase III enzyme that processes pre-miRNA; TRBP, TAR RNA binding protein; RISC, RNA-Induced silencing complex; 3' UTR, 3'untranslated region; AGO, argonaute; pre-miR, procursor miRNA hairpin.

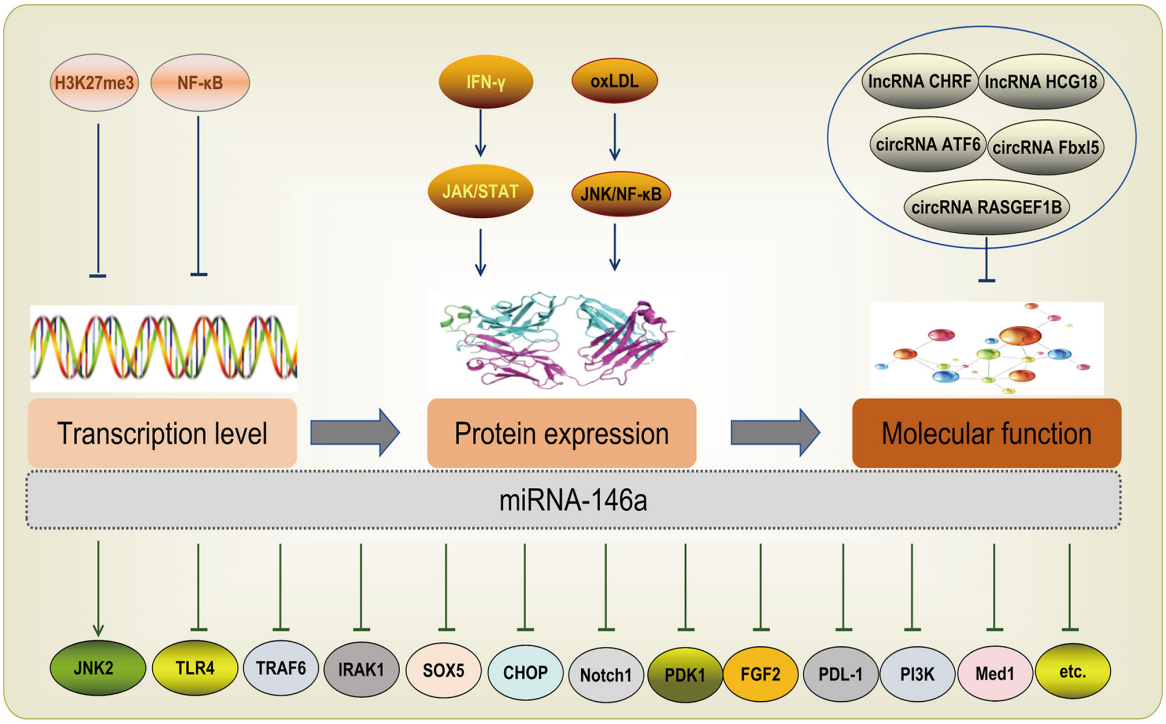


Figure 2. Regulation of miR-146a. The expression of miR-146a is mainly regulated by epigenetic modifications, transcription factors, interventions of upstream non-coding RNAs (such as lncRNAs and circRNAs), and multiple signaling pathways. It has a wide range of target genes, among which JNK2, CHOP, SOX5, TLR4, TRAF6, IRAK1, PDK1, FGF2, and PDL-1 have been identified. miR-146a, microRNA-146a; lncRNAs, long non-coding RNAs; circRNAs, circular RNAs; JNK2, c-Jun N-terminal kinase 2; CHOP, c/EBP-homologous protein; SOX5, SRY-box transcription factor 5; TLR4, Toll-like receptor 4; TRAF6, TNF receptor-associated factor 6; IRAK1, interleukin-1 receptor-associated kinase 1; PDK1, pyruvate dehydrogenase kinase isozyme 1; FGF2, fibroblast growth factor 2; PDL-1, programmed death-ligand 1; H3K27me3, histone H3 lysine 27 trimethylation; NF-κB, nuclear factor κ-light-chain-enhancer of activated B cells; IFN-γ, interferon-γ; JAK, Janus kinase; STAT, signal transducer and activator of transcription; oxLDL, oxidized low-density lipoprotein; PI3K, phosphoinositide 3-kinase; MED1, mediator complex subunit 1.

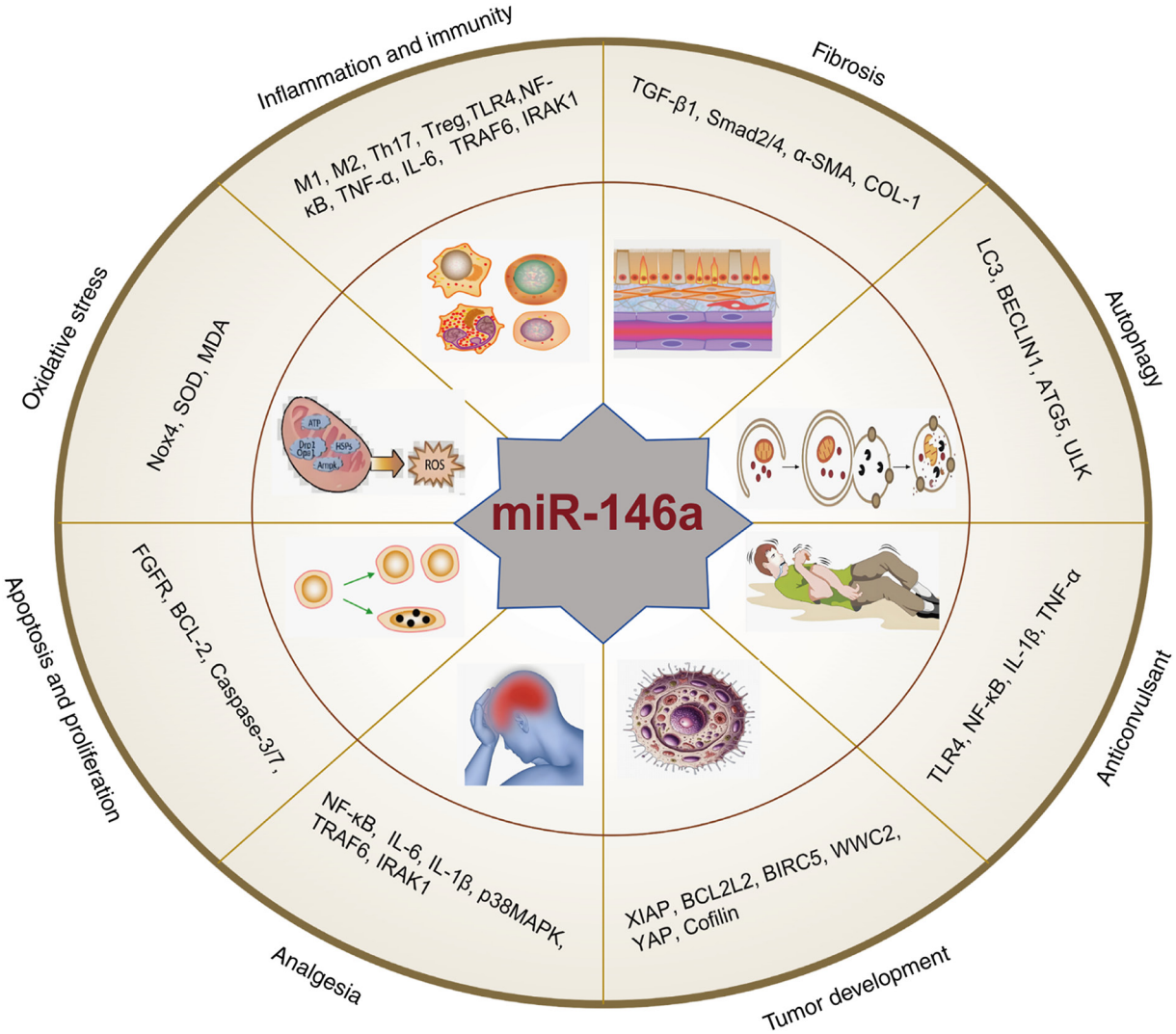


Figure 3. Biological functions of miR-146a. miR-146a is extensively involved in a variety of physiological and pathological processes, including immune regulation, inflammatory response, oxidative stress, apoptosis and proliferation, autophagy, anti-fibrosis, anti-convulsion, analgesia and antitumor, by regulating the expression of multiple molecules. miR-146a, microRNA-146a.

receptors (TLRs)/interleukin-1 receptor-associated kinase 1 (IRAK1)/TNF receptor-associated factor 6 (TRAF6) inflammatory signaling cascade, thereby further aggravating the downregulation of miR-146a (43,44). Within the chronic inflammatory microenvironment of osteoarthritis, IL-1β and TNF-α were shown to significantly increase the expression of miR-146a-5p in both chondrocytes and fibroblast-like synoviocytes. *In vitro* experiments with primary murine chondrocytes confirmed that IL-1β stimulation results in an ~4-fold increase in miR-146a-5p expression (45). In colorectal cancer, abundant inflammatory stimuli such as LPS and TNF-α within the tumor microenvironment were demonstrated to directly activate the transcription of miR-146a via the TLR4-NF-κB signaling axis, which serves as a well-characterized upstream regulatory pathway for miR-146a (46,47). Moreover, in intestinal epithelial cells, microenvironmental IL-17 signaling was found to modulate miR-146a expression through a TRAF6-dependent cascade, subsequently affecting the activity of prostaglandin E synthase 2 and mediating regulatory effects on tumor progression (48).

Overall, various pathological signals, including inflammatory factors and metabolites present in the disease microenvironment, can alter the expression level of miR-146a by impacting its transcription initiation, post-transcriptional processing and maturation, enabling adaptive responses to disease onset and progression.

## 3. Biological functions of miR-146a

Numerous downstream targets of miR-146a have been identified, including TLR4 (49), TRAF6 (50), SRY-box transcription factor 5 (SOX5) (51), c/EBP-homologous protein (CHOP) (52), JNK2 (53), notch receptor 1 (Notch1) (54), pyruvate dehydrogenase kinase isozyme 1 (PDK1) (38), and fibroblast growth factor 2 (FGF2) (55), which are widely implicated in various pathological and physiological processes such as immune regulation (8), inflammatory responses (9), oxidative stress (10), apoptosis and proliferation (11), autophagy (12), anti-fibrosis (13), anti-convulsant effects (14), analgesia (15), and antitumor activity (56) (Fig. 3).

The most well-established biological function of miR-146a involves its role in the negative regulation of innate immunity and inflammatory responses (57). Overexpression of miR-146a can induce a conversion of macrophages from a pro-inflammatory M1 phenotype to an anti-inflammatory M2 phenotype, as evidenced by reduced levels of pro-inflammatory factors such as TNF-α, IL-12, and IL-6, as well as decreased surface markers cluster of differentiation (CD)80 and CD86. Conversely, increased levels of anti-inflammatory factors such as arginase 1, C-C motif chemokine ligand (CCL)17, CCL22, and surface markers CD163 and CD206 (58) have been found, thereby contributing to the maintenance of immune homeostasis. Moreover, miR-146a directly has been shown to target the 3' UTR of the TRAF6 gene, resulting in a reduction of TRAF6 mRNA and protein expression levels. This inhibition was subsequently found to impede the activation of the TLR4/NF-κB pathway triggered by LPS, leading to decreased production of downstream inflammatory cytokines IL-6, TNF-α, and IL-8 (59). Further investigations have shown that overexpression of miR-146a can also target TRAF6 and IRAK1, thus inhibiting the activation of NF-κB and the release of inflammatory factors such as IL-1β, IL-6, and TNF-α (60), thereby mitigating tissue damage associated with excessive inflammatory responses. Inflammation and oxidative stress are two interrelated reactions that mutually promote one another during pathophysiological processes (61). Research by Wan and Li (62) demonstrated that overexpression of miR-146a can inhibit the expression of NADPH oxidase 4 (NOX4) protein, subsequently reducing ROS generation, oxidative stress [as indicated by lower superoxide dismutase (SOD) and malondialdehyde (MDA) levels], and inflammation.

Beyond its role in immune regulation and inflammation, miR-146a also participates in the regulation of fundamental biological processes, including cell apoptosis and proliferation, by targeting and modulating various downstream molecules, which are critical for maintaining the normal physiological functions of tissue cells (11,63). Increasing miR-146a expression can target fibroblast growth factor receptor protein expression, decrease the expression of the anti-apoptotic protein Bcl-2, activate the caspase-3/7 pathway, inhibit the proliferation of bronchial smooth muscle cells (SMCs), and promote their apoptosis (11). Furthermore, overexpression of miR-146a has been shown to reduce the expression of TRAF6 and NF-κB, thereby promoting the proliferation of osteoarthritis chondrocytes while inhibiting their apoptosis (63).

miR-146a plays a critical role in the regulation of autophagy. It can inhibit autophagic flux by suppressing the translation of autophagy-related proteins, while also being capable of activating autophagy in specific microenvironments, thus exerting opposing biological functions (64,65). In the context of hypoxia-induced chondrocyte autophagy, inhibition of miR-146a was shown to lead to the restoration of its downstream target genes, TRAF6 and IRAK1. The restoration of TRAF6 and IRAK1 subsequently increased the levels of the autophagy inhibitory protein Bcl-2, resulting in the inhibition of chondrocyte autophagy (64). Conversely, in human mononuclear leukemia cells (THP-1) responding to PM2.5-induced inflammatory responses, inhibition of miR-146a-5p was demonstrated to exacerbate the expression of IL-8 and autophagy-related genes (65). This indicated that the regulation of autophagy by miR-146a is highly specific to both the cell type and the microenvironment. Notably, two primary mechanisms contribute to these regulatory discrepancies. First, inherent heterogeneity exists in target gene expression profiles and canonical signaling pathways across different cell types. miR-146a selectively targets distinct downstream molecules, including TRAF6, IRAK1, and lipase A, lysosomal acid type, in varied cellular contexts, ultimately inducing opposing autophagy regulatory effects (64,66). Second, diverse microenvironmental stimuli, such as hypoxia, pathogen infection, and PM2.5 exposure, can reprogram the global transcriptional landscape of cells, altering the accessibility of miR-146a to its target sequences and consequently reversing the direction of downstream signal transduction, which leads to context-dependent discrepancies in autophagy regulation (65,67,68).

In addition to its role in autophagy, miR-146a also exhibits anti-fibrotic, anti-convulsant, and analgesic effects. Research has shown that overexpression of miR-146a-5p can directly target Smad4 and inhibit Smad2 phosphorylation, effectively blocking transforming growth factor (TGF)-β1/Smad signaling. This downregulation was demonstrated to inhibit proliferation and activation of hepatic stellate cells, thereby diminishing the pro-fibrotic effects of TGF-β1 and LPS (13). In a rat model of status epilepticus, the injection of a miR-146a agonist was found to significantly reduce inflammatory factors such as IL-1β and TNF-α, as well as TLR4 and NF-κB protein expression, consequently delaying the onset of convulsions and reducing their severity (14). Furthermore, a previous study demonstrated that increased levels of miR-146a-5p reduced microglial proliferation in the spinal dorsal horn, inhibited the activation of the NF-κB and p38 MAPK pathways, decreased the expression of TRAF6 and IRAK1 proteins, and downregulated the gene expression of pro-inflammatory cytokines IL-1β and IL-6, resulting in sustained analgesic effects in a spinal nerve ligation-induced neuropathic pain model (69).

miR-146a participates in tumor cell proliferation, invasion, and metastasis by targeting the expression of tumor-related genes (70-72). Overexpression of miR-146a-5p was shown to enhance the sensitivity of ovarian cancer cells to cisplatin and to promote apoptosis by targeting multiple anti-apoptotic genes such as baculoviral IAP repeat-containing protein 5 (BIRC5), B-cell lymphoma 2-like protein 2 (BCL2L2), and X-linked inhibitor of apoptosis protein (XIAP) (70). Conversely, another study revealed that extracellular vesicles derived from cervical cancer cells can deliver miR-146a-5p to inhibit WW and C2 domain-containing protein 2 (WWC2), subsequently activating downstream yes-associated protein (YAP) and regulating cofilin-mediated actin dynamics, thereby promoting cervical cancer metastasis (71). This bidirectional regulatory effect indicates the complexity of the mechanisms of miR-146a in tumor development and progression. In non-small cell lung cancer, the role of miR-146a also exhibits dual characteristics. Most studies indicate its downregulation and its involvement in anti-proliferation, pro-apoptosis, and inhibition of invasion and metastasis by targeting epidermal growth factor receptor (EGFR), sortilin 1 (SORT1), and macrophage migration inhibitory factor (MIF). Notably, it can significantly reduce tumor volume in *in vivo* xenograft models (73-75). However, in specific cell lines, miR-146a has also been shown to promote

tumor cell survival and migration by reducing the phosphorylation of NF-κB-p65 and downregulating TRAF6 (76,77). The dual regulatory features of miR-146a in colorectal cancer are even more varied; it can serve as a negative inflammatory regulator to restrict tumorigenesis while also promoting cell invasion and stem cell properties by targeting carboxypeptidase M and Numb (78,79). Additionally, exosome-carried miR-146a and miR-155 within the tumor microenvironment can synergistically activate the C-X-C chemokine receptor type 7 (CXCR7)-mediated metastasis pathway, which is closely associated with the activation of cancer-associated fibroblasts (80).

Overall, the bidirectional regulatory property of miR-146a across different tumors aligns with the inherent variations in cellular pathways and the reprogramming of microenvironmental signals. This property offers a promising new direction for subsequent stratified precision tumor therapy and the identification of targets for reversing drug resistance.

## 4. Role of miR-146a in the pathogenesis of cardiovascular diseases and endocrine metabolic disorders

*Cardiovascular system diseases*

*Sepsis-induced cardiomyopathy (SIC).* SIC refers to reversible myocardial dysfunction resulting from a systemic inflammatory response triggered by severe infection and is a common complication of sepsis or septic shock (81). As a classic inflammation-related miRNA, the functional polymorphism of miR-146a influences individual susceptibility to severe sepsis by regulating the activation of inflammatory pathways (82). A study involving a Chinese population revealed that in patients with severe sepsis, the frequency of the C allele and CC genotype of the miR-146a gene rs2910164 was significantly higher compared with that in healthy controls (82). This finding suggests a close relationship between polymorphisms in this gene and the risk of severe sepsis. Moreover, the expression levels of miR-146a in peripheral blood mononuclear cells of patients with severe sepsis were found to be markedly reduced, whereas the expression of its target genes, TRAF6 and IRAK1, was significantly increased (82). The downregulation of miR-146a disrupts its negative regulatory effect on downstream inflammatory target genes, leading to the excessive release of pro-inflammatory factors and subsequent myocardial damage. This conclusion is supported by a study conducted by Gao *et al* (83), which utilized cecal ligation and puncture (CLP) to establish a mouse model of septic cardiac dysfunction. The researchers delivered lentivirus expressing miR-146a to the myocardium via the right carotid artery (83). The results indicated that increased myocardial miR-146a restrained NF-κB activation by inhibiting IRAK1 and TRAF6 expression, ultimately reducing the levels of inflammatory factors (IL-6, TNF-α, IL-1β) and myocardial adhesion molecules [vascular cell adhesion molecule 1 (VCAM-1) and intercellular adhesion molecule 1 (ICAM-1)], thereby inhibiting neutrophil and macrophage infiltration into the myocardium and mitigating the progression of SIC (83). Despite providing critical support for the cardioprotective effect of miR-146a, several limitations were present in this study. First, the observation time window was relatively short: Cardiac function and inflammatory indicators were primarily evaluated 6 h post-CLP surgery, without exploring the long-term effects of miR-146a intervention on cardiac remodeling and functional recovery. Second, while the method of intramyocardial injection of lentivirus is effective, it presents challenges regarding tissue specificity, safety, and future clinical translation. Third, the study verified relevant effects using a single CLP-induced peritonitis sepsis model, and findings have not been replicated in other classic sepsis models, such as LPS intravenous injection-induced endotoxin shock (83), thus necessitating further validation of the generalizability of the conclusions.

In addition to its regulatory role in inflammation, research has confirmed that miR-146a serves as a key molecule governing cardiac energy metabolic homeostasis. Increasing the expression of miR-146a may promote energy metabolism disorders in cardiomyocytes (84). Conversely, reducing miR-146a levels may exacerbate myocardial energy metabolism disorders by downregulating dihydrolipoamide S-succinyltransferase (DLST), potentially increasing the risk of sepsis progressing to severe disease and inducing SIC (84) (Fig. 4 and Table SI).

*Myocardial ischemia-reperfusion injury (MIRI).* Following MIRI, the expression of miR-146a in myocardial tissues and cells was shown to be significantly downregulated (85). The regulatory mechanisms of miR-146a are complex and primarily involve protective effects mediated through various targets.

On one hand, a growing body of evidence has confirmed that exogenous supplementation of miR-146a has prominent cardioprotective effects. By specifically regulating neurofibromin 2 (NF2) and subsequently activating the downstream Ras-related C3 botulinum toxin substrate 1 (Rac1)/p21-activated kinase 1 (PAK1) signaling axis, this intervention was found to significantly enhance vascular endothelial growth factor (VEGF) secretion and microangiogenesis capacity in the rat heart, ultimately providing therapeutic benefits against myocardial ischemia-reperfusion (I/R) injury (86). This protective effect has been further validated in both cellular and *in vivo* experimental systems. In a mouse model of myocardial I/R injury and in isolated cardiomyocyte hypoxia/reoxygenation models, intervention with miR-146a mimics effectively silenced NOX4 expression and inhibited its enzymatic activity. This resulted in reduced excessive ROS production, blockage of the overactivation of the p38 signaling pathway, and ultimately alleviated MIRI from an oxidative stress perspective (85).

On the other hand, studies are also focusing on part of endogenous miR-146a and non-coding RNAs that interact with it. Mechanistic research targeting MIRI has confirmed that circRNA Fbxl5 directly sequesters and depletes intracellular miR-146a in cardiomyocytes through the ceRNA mechanism, which abolishes the translational repression of mediator complex subunit 1 (MED1) mediated by miR-146a, ultimately promoting the progression of cardiomyocyte apoptosis (41). Functional pathways indicate that endogenous miR-146a, regulated by circRNA Fbxl5, exerts its effects by targeting the MED1/thyroid hormone receptor-associated protein 220 (TRAP220) signaling axis. This regulation increases the ratio of the pro-apoptotic protein Bax to the anti-apoptotic protein Bcl-2, activating the apoptotic executor

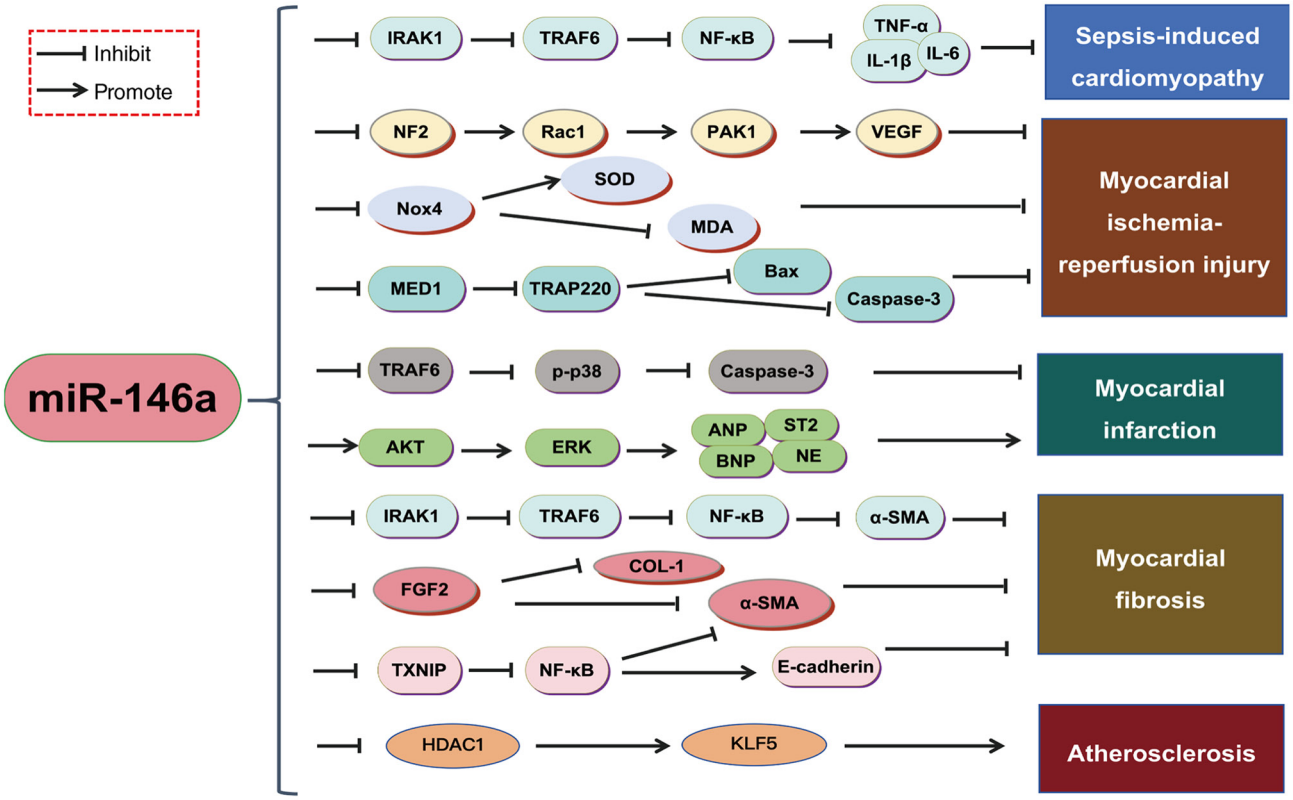


Figure 4. Molecular mechanism of miR-146a in cardiovascular system diseases. miR-146a, microRNA-146a; AKT, protein kinase B; ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; caspase-3, cysteine aspartic acid-specific proteinase-3; COL-1, collagen type I; E-cadherin, epithelial cell adhesion molecule; ERK, extracellular signal-regulated kinase; FGF2, fibroblast growth factor 2; HDAC1,histone deacetylase 1; IRAK1, interleukin-1 receptor-associated kinase 1; IL-1β, interleukin-1β; IL-6, interleukin-6; KLF5, Krüppel-like factor 5; MDA, malondialdehyde; MED1, mediator complex subunit 1; MDA, malondialdehyde; NF-κB, nuclear factor κ-light-chain-enhancer of activated B cells; NF2, neurofibromin 2; Nox4, NADPH oxidase 4; NE, norepinephrine; PAK1, p21-activated kinase 1; Rac1, ras-related C3 botulinum toxin substrate 1; SOD, superoxide dismutase; ST2, suppression of tumorigenicity 2; TNF-α, tumor necrosis factor-α; TXNIP, thioredoxin-interacting protein; TRAF6, tumor necrosis factor receptor-associated factor 6; TRAP220, thyroid hormone receptor-associated protein 220; VEGF, vascular endothelial growth factor; α-SMA, α-smooth muscle actin.

caspase-3 and fully initiating the apoptotic signaling cascade in cardiomyocytes (87).

In addition to circRNAs, lncRNAs also play critical roles as upstream molecules that modulate the functional activity of miR-146a in cardiomyocytes, collectively forming a complex non-coding RNA regulatory network during the progression of MIRI. This regulatory paradigm has been fully validated through functional studies involving lncRNA SOX2-OT. Bidirectional validation using an *in vitro* oxygen-glucose deprivation/reoxygenation system of H9C2 cardiomyocytes and an *in vivo* rat MIRI model has confirmed that the injury-promoting effect of SOX2-OT is entirely dependent on its sequestration and depletion of miR-146a-5p (88) Silencing of SOX2-OT was shown to alleviate myocardial cell apoptosis, reduce inflammatory factors (TNF-α, IL-6, and IL-1β), and decrease oxidative stress (reducing MDA and increasing SOD activity) by upregulating miR-146a-5p (88) (Fig. 4 and Table SI).

Overall, current studies systematically elucidate the core cardioprotective role of miR-146a in MIRI from two dimensions: exogenous intervention and endogenous regulation. Exogenous supplementation of miR-146a can mitigate I/R injury through multiple pathways, while the function of endogenous miR-146a is directly modulated by a regulatory network composed of circRNAs and lncRNAs. Collectively, these insights provide novel theoretical foundations for clinical targeted therapy of MIRI. However, existing studies still lack evaluations of long-term efficacy and safety, and the prospects for clinical translation remain to be further explored.

*Myocardial infarction (MI).* Research has indicated that miR-146a expression in the blood of patients with ST-segment elevation myocardial infarction (STEMI) is significantly higher than in healthy controls, suggesting that miR-146a may serve as an alternative blood biomarker for predicting poor prognosis in STEMI (18,89). Huang *et al* (89) found that in mouse models of acute MI and rat cardiomyocyte hypoxia models *in vitro*, both miR-21 and miR-146a (mimetic) could individually reduce myocardial cell apoptosis, decrease infarct size, enhance cardiac function (including improvements in ejection fraction and shortening rate), and lower serum lactate dehydrogenase activity (89). However, the combination of these miRNAs proved to be more effective than either alone. Further investigation into the underlying mechanisms revealed that miR-21 activates AKT by inhibiting its target PTEN, thereby indirectly reducing the phosphorylation of p38 MAPK, while miR-146a directly inhibits TRAF6, blocking p38 phosphorylation (p-p38) activation (89). Together, these effects significantly enhance the inhibition of p-p38 and its downstream pro-apoptotic protein, caspase-3, providing a

more effective defense against ischemia- or hypoxia-induced cardiomyocyte death (89). Another study showed that exosomes combined with miR-126 and miR-146a could promote myocardial repair following MI by enhancing angiogenesis and reducing fibrosis (90). However, research by He *et al* (91) suggested that inhibiting miR-146a could improve cardiac dysfunction, reduce neurohormonal activation [as indicated by decreased levels of atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), suppression of tumorigenicity 2 (ST2), and norepinephrine (NE)], and mitigate myocardial fibrosis (by lowering collagen I/III) after MI in rats, achieved through the regulation of the AKT/ERK signaling pathway, ultimately alleviating heart failure (91) (Fig. 4 and Table SI).

The dual and contradictory effects of miR-146a (exhibiting both protective and detrimental roles) in MI are not due to experimental discrepancies; rather, they reflect stage-specific and cell-type-specific outcomes influenced by the various pathological phases of MI, target cell categories, animal models, and intervention strategies (89-91).

During the early acute ischemic phase of MI (within 3 days post-ligation, characterized by ischemia, acute inflammation, and extensive cardiomyocyte apoptosis) (92), miR-146a suppresses NF-κB/p38-mediated inflammation and cardiomyocyte apoptosis by targeting TRAF6. Whether used alone or in combination with miR-21 and miR-126, miR-146a can reduce infarct size and promote endothelial angiogenesis, thus exerting significant cardioprotective effects (89,90). However, as the condition progresses to the chronic ventricular remodeling and heart failure phase (4 weeks or later post-MI), where core pathological manifestations include myocardial fibrosis, overactivation of the neuroendocrine system, and impaired cardiomyocyte calcium homeostasis (93), persistently elevated levels of miR-146a affect cardiac fibroblasts. This overexpression abnormally activates the AKT/ERK pathway, facilitating collagen deposition, disrupting cardiomyocyte calcium homeostasis, inhibiting myocardial contractile function, and ultimately exacerbating myocardial fibrosis and heart failure (91).

Significant cell-type specificity characterizes the functional actions of miR-146a. When targeting cardiomyocytes and endothelial cells, miR-146a predominantly exerts anti-inflammatory and pro-repair effects (89,90); however, sustained activity on fibroblasts leads to fibrotic responses (91). These phenotypic discrepancies are further amplified by variations in experimental systems: The short-term mouse left anterior descending ligation model, which focuses solely on the acute phase, exclusively highlights the protective effect of miR-146a (89), whereas the long-term rat heart failure model, which addresses remodeling injuries, highlights its detrimental impact (91). Local short-term administration through exosomes results in minimal long-term accumulation and exhibits extremely low side effects (90). Conversely, long-term systemic injection of agomiR via the tail vein has been show to lead to persistently high expression levels of miR-146a in myocardial tissue (91), exacerbating adverse cardiac remodeling. Under regimens involving short-term local delivery or combined use with other cardioprotective miRNAs, miR-146a generally confers beneficial effects (89,90), whereas long-term systemic overexpression reveals its pro-remodeling detrimental role (91).

Given these observations, miR-146a cannot be simplistically categorized as either a protective or detrimental molecule in the context of MI. Research conducted by Chen *et al* (94), revealed that exosomes with low expression of miR-146a-5p extracted from MI tissue can, on one hand, promote the polarization of macrophages toward the M1 type while inhibiting polarization to the M2 type, aggravating the inflammatory response. On the other hand, miR-146a-5p can exert an anti-inflammatory effect by targeting TRAF6 (94). These findings suggest that the function of miR-146a is highly dependent on specific spatial and temporal contexts and cell types, necessitating a comprehensive evaluation in conjunction with disease time windows, target cell types, and administration regimens (89-91). This insight carries significant implications for clinical researchers: During the acute phase of MI, local delivery of miR-146a agonists combined with synergistic intervention using miR-21 or miR-126 should be considered to mitigate acute injury. By contrast, during the chronic heart failure stage, the use of inhibitors to downregulate miR-146a may be beneficial in blocking fibrosis and improving myocardial contractile function.

*Myocardial fibrosis*. Myocardial fibrosis is a common pathological change observed in the progression of various cardiovascular diseases toward end-stage conditions (95). Studies have indicated that miR-146a primarily serves a protective regulatory role in the myocardial fibrosis process. This role is mainly achieved by targeting and regulating downstream inflammatory signaling pathway molecules and fibrosis-related proteins, thereby inhibiting endothelial-mesenchymal transition (EndMT) and fibroblast activation (55,96,97) (Fig. 4 and Table SI). In a rat model of constrictive pericarditis with myocardial fibrosis, an increase in miR-146a expression was noted at 8 weeks, followed by a decrease at 16 weeks. Overexpression of miR-146a was found to inhibit the expression of IRAK1, TRAF6, p-NF-κB and α-smooth muscle actin (SMA) in rat cardiac fibroblasts induced by LPS, thereby mitigating myocardial fibrosis (96). This study is the first to reveal the dynamic expression pattern of miR-146a throughout the progression of constrictive pericarditis and its functional role in regulating myocardial fibrosis, indicating its potential as a biomarker for disease progression and as a therapeutic target (96). However, this research is primarily based on animal and cellular models without validation in human samples, and the specific regulatory mechanisms underlying the dynamic expression changes of miR-146a have not been thoroughly explored.

The rat myocardial fibrosis model induced by isoproterenol further supports the antifibrotic protective effect of miR-146a (55). A significant downregulation of miR-146a-5p was observed in the myocardial tissues of the model animals. *In vitro* experiments demonstrated that overexpression of miR-146a-5p in cardiac fibroblasts could directly target and suppress FGF2, leading to a reduction in the synthesis of α-SMA and type I collagen, which consequently retards fibrotic progression (55). However, existing studies have only identified FGF2 as a direct target of miR-146a-5p, and the complete downstream signaling cascade mediated by miR-146a-5p following FGF2 repression remains poorly characterized.

Consistent findings have been reported in MI-related hypoxic injury systems, as well as in drug-induced fibrosis models (97). Research conducted by Wang *et al* (97) revealed that miR-146a-5p expression was significantly decreased in both hypoxic human cardiac microvascular endothelial cells and cardiac tissues from MI mice (97). miR-146a-5p was shown to target thioredoxin-interacting protein (TXNIP) to inhibit the activity of the NF-κB pathway, upregulate the endothelial marker E-cadherin, and downregulate the mesenchymal marker α-SMA, thereby obstructing the process of EndMT and ultimately alleviating myocardial fibrotic injury induced by the hypoxic microenvironment (97). This study elucidated that the miR-146a-5p/TXNIP axis modulates post-MI cardiac fibrosis by regulating EndMT, presenting a novel perspective for understanding the mechanisms of fibrosis following MI.

*Atherosclerosis*. Levels of miR-146a, IL-6, and TNF-α in the peripheral blood of patients with carotid atherosclerosis have been shown to be significantly higher than those in healthy controls, and there exists a positive correlation with the degree of carotid artery stenosis (23). This suggests that miR-146a may be involved in the development of atherosclerosis. Research conducted on mouse models of atherosclerosis has elucidated the specific mechanisms by which miR-146a-3p operates (98). It was observed that miR-146a-3p expression surged in the aortic wall tissue of atherosclerostic mice (98). Knocking down miR-146a-3p resulted in the upregulation of histone deacetylase 1 and inhibitor of NF-κB α (IKBα) expression while inhibiting the expression of Krüppel-like factor 5. These changes ultimately led to reduced plasma lipid levels, decreased inflammatory factors in serum, and inhibited apoptosis of aortic wall cells, promoting the stability of atherosclerotic plaques (98). This finding suggests that miR-146a-3p may play a critical role in promoting plaque instability in disease states and that its inhibition could help alleviate the disease.

At the cellular level, oxLDL can enhance miR-146a expression in macrophages via its receptor lectin-like oxLDL receptor-1 (LOX-1) and the downstream JNK and NF-κB signaling pathways (35). Elevated miR-146a targets TRAF6 and IRAK1 to inhibit the NF-κB signaling pathway, resulting in the downregulation of CD80 and CD86. This suppresses macrophage maturation and M1-type pro-inflammatory activation, reduces the release of pro-inflammatory cytokines, and establishes a negative feedback loop, thereby limiting excessive local inflammation within atherosclerotic plaques. This provides novel insights into the complex interplay between inflammation and the miRNA regulatory network in atherosclerosis (35). In addition, abnormal proliferation and migration of vascular SMCs (VSMCs) are critical pathological links in atherosclerotic plaque formation (99). Inhibiting miR-146a expression can stimulate the proliferation of rat VSMCs by downregulating p53 and upregulating cyclin D1 (100). Notably, the effects of miR-146a appear to be cell-specific. Research by Cheng *et al* (101) demonstrated that in bone marrow cells, miR-146a inhibits NF-κB signaling, prevents hematopoietic stem cell exhaustion, and maintains the pool of pro-atherosclerotic cells. In vascular endothelial cells, miR-146a was also shown to inhibit NF-κB signaling, limit endothelial activation and monocyte recruitment, and help alleviate the promotion of atherosclerosis (101) (Fig. 4 and Table SI).

Overall, miR-146a exerts seemingly opposing regulatory effects on atherosclerosis across endothelial cells, macrophages, and bone marrow hematopoietic cells. The fundamental reason for this lies in its unified molecular function, while significant differences exist in the pathological roles, downstream effector pathways, and long-term compensatory responses of different cell types within the pathological cascade of atherosclerosis (35,100,101).

From a molecular perspective, miR-146a consistently targets TRAF6 and IRAK1 to inhibit the NF-κB inflammatory pathway, exhibiting no bidirectional activity switching. The observed phenotypic discrepancies arise from the cellular microenvironment and the regulatory networks of target genes (102). In endothelial cells, excessive NF-κB activation was shown to lead to substantial secretion of adhesion molecules such as ICAM-1 and VCAM-1, which facilitate the recruitment of pro-inflammatory monocytes into the vascular intima, a critical step in the initiation of atherosclerosis (103). By inhibiting endothelial NF-κB, miR-146a was found to alleviate endothelial activation and monocyte infiltration, thereby exerting an anti-atherosclerotic effect (101). However, a temporal cascade discrepancy exists in the functional effects on bone marrow hematopoietic cells: Loss of miR-146a resulted in persistent, uncontrolled NF-κB activation within the bone marrow, stimulating significant proliferation of hematopoietic stem cells and a transient increase in pro-inflammatory monocytes in the short term. This excessive inflammatory stimulation, over the long term, was shown to lead to hematopoietic stem cell exhaustion (101). Compensatory extramedullary hematopoiesis failed to offset the loss of bone marrow function, resulting in a marked reduction in circulating lymphocyte antigen 6 complex locus C-high ($Ly6C^{hi}$) pro-atherosclerotic monocytes and neutrophils (101). Concurrently, miR-146a was revealed to target SORT1 to regulate lipid metabolism; its deletion in the bone marrow upregulated hepatic SORT1, thereby reducing circulating very-low-density lipoprotein (VLDL) and LDL cholesterol levels and decreasing the supply of lipid substrates for plaques, ultimately mitigating overall atherosclerotic lesions (101). Furthermore, miR-146a in macrophages can suppress cell maturation and local inflammation (35), while in SMCs, it influences cell proliferation through regulation of the p53/cyclin D1 axis. The distinctive target gene profiles present in various cell types amplify these functional discrepancies (100).

In summary, miR-146a exhibits a singular inhibitory effect on the NF-κB signaling pathway. In endothelial cells, inflammation suppression directly impedes the initiation of atherosclerotic plaques; in macrophages, it establishes an endogenous anti-inflammatory negative feedback loop that prevents excessive pro-inflammatory activation, thereby protecting the vascular wall. Conversely, in bone marrow cells, the long-term uncontrolled inflammation resulting from miR-146a deficiency prompts hematopoietic failure and disrupts the supply of pro-inflammatory cells, ultimately yielding opposing pathological outcomes.

*Endocrine and metabolic system*

*Diabetes*. Diabetes has long been a focal point of clinical and basic research. As a classic inflammation-related miRNA, miR-146a has been implicated in the onset and progression of diabetes (104,105). Population-based evidence across different diabetes subtypes indicates aberrant expression of miR-146a in both type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) populations. In a case-control study involving 177 pairs of Egyptian patients with T1DM and healthy controls, serum miR-146a expression was significantly downregulated in patients (104). A meta-analysis encompassing multiple cohort studies further confirmed that miR-146a expression levels were markedly lower in patients with T2DM compared with healthy individuals (105). Interventional studies have enhanced the understanding of the dynamic characteristics of miR-146a in the pathological regulation of diabetes. In a clinical trial conducted by Shokri-Mashhadi *et al* (106), 44 patients with T2DM were randomly divided into two groups: Those receiving 8 mg of oral astaxanthin (n=22) and those receiving a placebo (n=22) daily. The results demonstrated that astaxanthin supplementation significantly reduced plasma MDA and IL-6 levels compared with the placebo group. Additionally, astaxanthin significantly downregulated miR-146a expression levels, but did not have a statistically significant effect on miR-126 expression (106). Nevertheless, all these studies are single-center investigations with relatively small regional sample sizes. The meta-analysis included only 12 studies with a total of <700 cases (105), the interventional trial enrolled merely 44 patients (106), and the T1DM-related study involved 177 subjects per group at a single center (104). None have been validated through multi-center, trans-ethnic large cohorts. Moreover, existing studies have primarily focused on the correlation between miR-146a expression and diabetes, as well as inflammatory markers, without incorporating cellular and animal experiments to elucidate the upstream and downstream regulatory pathways (104-106) Consequently, it remains unclear whether miR-146a functions as a pathogenic inducer of diabetes or is merely a concomitant consequence of inflammatory injury, leading to a relatively superficial understanding of its molecular mechanisms. Therefore, future research should include multi-center large-sample cohort studies combined with functional validation of miR-146a in cellular and animal models.

Gene polymorphisms of non-coding RNA can influence autoimmune regulation and the inflammatory response by altering the expression or function of non-coding RNA, thereby affecting disease risk (107,108). Concerning the association between miR-146a gene polymorphism and diabetes susceptibility, existing studies have not reached a consensus. A meta-analysis conducted by Cheng *et al* (109) encompassed four studies, including a total of 2,069 patients and 1,950 controls. The results suggested no strong correlation between the miR-146a rs2910164 polymorphism and T2DM susceptibility. However, this conclusion carries certain limitations: It is constrained by the small number of included studies and insufficient overall sample size. Additionally, significant heterogeneity exists among the studies regarding factors such as the ethnicity of the study population, genotyping methods, and the disease course of subjects; thus, the influence of publication bias on pooled results cannot be entirely ruled out (109). Subsequent investigations targeting the T1DM population yielded different association evidence. A case-control study involving 92 Egyptian children with T1DM and 92 healthy controls indicated that the AG genotype, GG genotype and G allele at the miR-146a rs57095329 locus were all significantly associated with an increased risk of T1DM (110). Nevertheless, this study also has apparent limitations. The overall sample size was relatively small, and the study population comprised only a single Egyptian ethnic group. Therefore, the association between this locus polymorphism and T1DM susceptibility necessitates further verification through larger-scale, multi-population cohort studies (110).

*Complications of diabetes*. Diabetes complications include microvascular diseases, diabetic nephropathy, peripheral neuropathy, and diabetic foot, among others (111,112). Compared with patients without diabetic complications, those with one or more diabetic complications exhibited significantly lower serum levels of miR-146a-5p, suggesting that miR-146a-5p may serve as a novel candidate biomarker for such complications (113) (Fig. 5 and Table SII).

*Vascular diseases*. Diabetic macrovascular and microvascular diseases represent the primary pathological basis for systemic multi-organ damage associated with diabetes, with the core pathological alterations closely linked to vascular endothelial cell damage (114,115). In the context of high glucose-induced vascular endothelial cell damage, NF-κB serves as a pivotal inflammatory transcription factor that can initiate the expression of various downstream pro-inflammatory factors, thereby accelerating endothelial cell dysfunction (116,117). Research by Kamali *et al* (43) designed a human umbilical vein endothelial cell (HUVEC) model cultured in high glucose to investigate the effects of varying miR-146a expression levels on the protein and mRNA expression of NF-κB. The study found that, under high glucose stimulation, both miR-146a and its target proteins, TRAF6 and IRAK1, exhibited upregulation in HUVECs, while NF-κB gene expression and protein activity (phosphorylated NF-κB p65) also significantly increased (43). However, following the inhibition of miR-146a expression in a high-glucose environment, NF-κB protein activity significantly increased, yet its mRNA expression level unexpectedly decreased (43). Simultaneously, inhibiting miR-146a led to also a substantial upregulation of IRAK1 and TRAF6 mRNA expression levels. These results imply that the upregulation of miR-146a in HUVECs during the early stages of high glucose may function as a negative feedback protective mechanism, attempting to regulate NF-κB activation by inhibiting TRAF6 and IRAK1 to avert excessive inflammatory responses (43).

In high glucose-induced human aortic endothelial cells (HAECs), expression of miR-146a-5p was significantly downregulated, which was associated with increased levels of IRAK1 and ICAM-1 (44). Transfection with miR-146a-5p mimics reduced high glucose-induced expression of VCAM-1 and ICAM-1, as well as IRAK1, along with monocyte adhesion. These findings suggest that miR-146a-5p is involved in the regulation of endothelial inflammation induced by high glucose through the modulation of IRAK1 (44). Consistent with these results, significantly decreased expression of miR-146a was also observed in the aortas of diabetic rats compared

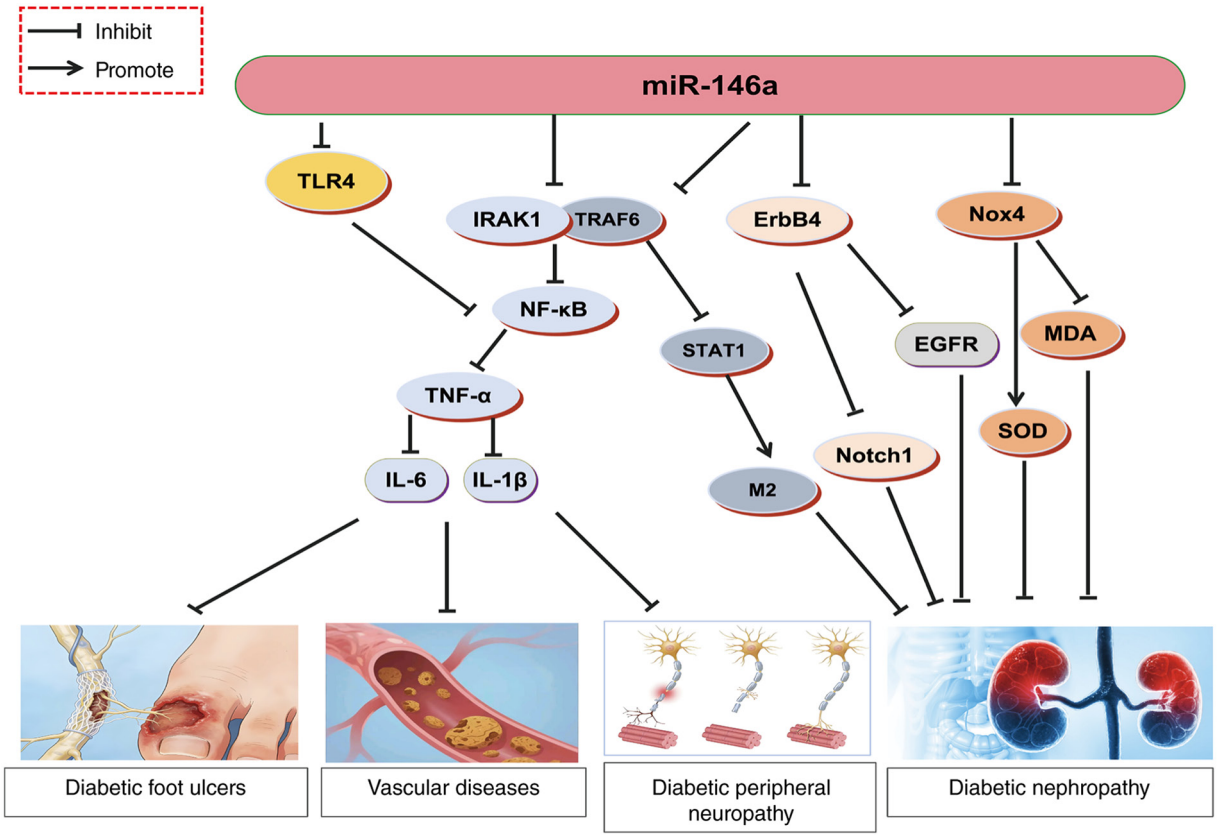


Figure 5. Molecular mechanism of miR-146a in diabetic complications. miR-146a, microRNA-146a; EGFR, epidermal growth factor receptor; ErbB4, erythroblastic leukemia viral oncogene homolog 4; IL-1β, interleukin 1β; IL-6, interleukin 6; IRAK1, interleukin-1 receptor-associated kinase 1; M2, macrophage M2 phenotype; MDA, malondialdehyde; NF-κB, nuclear factor κ-light-chain-enhancer of activated B cells; Nox4, NADPH oxidase 4; Notch1, notch receptor 1; SOD, superoxide dismutase; STAT1, signal transducer and activator of transcription 1; TLR4, Toll-like receptor 4; TNF-α, tumor necrosis factor-α; TRAF6, TNF receptor-associated factor 6.

with healthy rats, which was associated with elevated mRNA levels of IRAK1, TRAF6, NF-κB, and increased protein levels of inflammatory factors such as IL-1β, IL-6, TNF-α, and ICAM-1 (118) One month after treatment of diabetic rats with troxerutin, blood glucose and insulin levels improved; additionally, compared with the diabetic group, expression of inflammatory genes and pro-inflammatory mediators was substantially reduced, and miR-146a levels were elevated (118). Thus, troxerutin may exert anti-inflammatory and vascular protective effects by modulating the miR-146a/NF-κB signaling pathway (118). This research provides novel insights into the molecular mechanisms underlying the prevention and treatment of diabetic vascular complications through troxerutin (Fig. 5 and Table SII).

Of note, three studies have reported conflicting results regarding the upregulation or downregulation of miR-146a in blood vessels under high-glucose or diabetic conditions. The fundamental reason for these discrepancies lies in variations in experimental models, stimulation durations, vascular cell types, and disease stages, which capture distinct dynamic phases of the miR-146a/NF-κB negative feedback loop. These variations can be summarized in three main aspects (43,44,118).

First, the duration of high-glucose stimulation and the disease stage are critical factors. miR-146a functions as an anti-inflammatory negative feedback molecule downstream of NF-κB. When venous endothelial cells are stimulated by high glucose for a brief period of 24 h (43), NF-κB is mildly activated, resulting in compensatory upregulation of miR-146a. By contrast, prolonged high glucose exposure for 48 h in aortic endothelial cells (44) or in 10-week long-term diabetic rats (118) leads to oxidative stress and the accumulation of advanced glycation end products, which disrupt the miRNA maturation pathway, resulting in miR-146a depletion and reduced expression, ultimately impairing the anti-inflammatory feedback response. Even if miR-146a is upregulated during the acute phase, its target gene degradation rate cannot keep pace with the transcriptional increase of IRAK1 and TRAF6, allowing it only to partially mitigate inflammation.

Second, inherent response differences among vascular endothelial cell subtypes are relevant. Experiments utilized HUVECs (43) and HAECs (44,118), respectively. Venous endothelial cells, subjected to lower blood flow shear forces, experience milder glucose-induced injury, which can readily induce compensatory increases in miR-146a (43). By contrast, arterial cells, subjected to the dual insults of blood flow shear stress and high glucose, are more prone to impaired miR-146a synthesis and subsequent downregulation (44,118).

Lastly, *in vitro* microenvironments differ significantly from those *in vivo*. *In vitro* experiments typically involve simple high glucose treatment with few confounding factors (43). In diabetic rats, conditions include concomitant insulin deficiency, systemic chronic inflammation, and coordinated

multi-cellular injury, all of which can deplete miR-146a levels. Consequently, miR-146a is generally expressed at lower levels in vascular tissues *in vivo*, but troxerutin can restore its expression by inhibiting excessive NF-κB activation and facilitating the repair of miRNA synthesis (118).

In summary, the upregulation and downregulation of miR-146a reflect the dynamic progression of vascular inflammation, transitioning from early compensation to long-term decompensation, with differences in experimental models accounting for discrepancies in detection results.

*Diabetic peripheral neuropathy (DPN)*. The pathogenesis of DPN remains incompletely understood. Existing research suggests that chronic inflammatory responses play a critical role in the onset and progression of DPN (119,120). In a study comparing control and T2DM groups, significant decreases in sciatic nerve conduction velocity (NCV) and miR-146a expression levels were observed in the DPN group, along with marked increases in the expression of TNF-α, IL-1β, and NF-κB (121). This indicates that miR-146a is involved in the pathogenesis of DPN, with its expression level closely linked to the inflammatory responses that exacerbate sciatic nerve injury (121). Another mechanistic study further enriched these conclusions (122). In db/db diabetic mice, miR-146a was significantly downregulated in peripheral nerves and monocytes (122). Following treatment with miR-146a mimics, serum and tissue levels of miR-146a increased, which corresponded with improved NCV and footpad/sciatic nerve blood perfusion, as well as restored nerve density and myelin morphology (122). Molecular mechanism research revealed that miR-146a reduces the expression of inflammatory target genes (TRAF6 and IRAK1), inhibits NF-κB signaling (specifically, p65 protein levels), shifts macrophages to an anti-inflammatory M2 phenotype, and decreases TNF-α and IL-1β levels, thereby mitigating neurovascular damage induced by hyperglycemia (122) (Fig. 5 and Table SII).

Moreover, a clinical study involving 150 subjects (49 patients with T2DM with DPN, 51 patients with T2DM without DPN, and 50 healthy controls) (123) observed that miR-146a expression levels in the peripheral blood of patients with T2DM were significantly lower than those of healthy controls, and that patients with T2DM and DPN had notably lower expression levels than their counterparts with simple T2DM (without DPN) (123). This suggests that miR-146a may serve as a valuable biomarker for the prognosis and diagnosis of DPN. However, this study is limited by its single-center design and relatively small sample size, which complicates the generalization of these findings to diabetic populations across different regions and ethnic groups (123).

*Diabetic nephropathy*. Diabetic nephropathy represents the most severe complication of diabetes (124). Regarding the role of miR-146a in diabetic nephropathy, existing studies have constructed a comprehensive stepwise evidence chain, progressing from population baseline characterization and *in vivo* animal functional validation to *in vitro* cellular mechanism dissection and exploration of therapeutic intervention strategies (37,125).

In terms of baseline expression characteristics, clinical samples and animal models demonstrate high consistency; specifically, the expression level of miR-146a in glomerular tissues from both diabetic patients and diabetic model mice shows a significant decline, suggesting a potential association between the abnormal expression of this molecule and the occurrence and progression of diabetic kidney disease (37). Subsequent gain-of-function and loss-of-function experiments have directly verified this causal relationship. In diabetic mice with miR-146a knockout, there was a significant increase in proteinuria observed, alongside marked aggravation of glomerular pathological damage. Conversely, artificial upregulation of miR-146a expression can protect podocyte, key functional cells within the glomeruli, by targeted inhibition of the Erb-B2 receptor tyrosine kinase (ErbB4)-Notch-1 signaling pathway, thus countering the pathological damage induced by a high-glucose microenvironment (37).

To avoid interference from miR-146a derived from other cell types and to focus specifically on the function of this molecule in podocytes, subsequent research constructed podocyte-specific miR-146a knockout mice (Pod-miR146a$^{-/-}$) and induced renal injury using three modeling approaches with distinct mechanisms: Low-dose LPS, nephrotoxic serum, and streptozotocin (125). Consistent conclusions emerged across different injury models, showing that podocyte-specific deletion of miR-146a further exacerbated the severity of proteinuria and glomerular injury in mice with diabetic kidney disease (125). Mechanistic investigations revealed that miR-146a in podocytes can simultaneously target and inhibit two injury-promoting signaling pathways, ErbB4/EGFR and TGF-β-Smad3, thereby maintaining the structural and functional homeostasis of podocytes. The loss of function of this molecule accelerates the pathological progression of diabetic kidney disease (125). However, this study did not elucidate how the upregulation of ErbB4/EGFR specifically activates the TGF-β-Smad3 pathway, highlighting the need for further investigation into the underlying mechanism (125). Beyond the mechanisms in glomerular podocytes, studies at the renal tubular level have further enriched the protective network of miR-146a. In a high-glucose-induced injury model involving human renal tubular epithelial HK-2 cells, overexpression of miR-146a significantly inhibited NOX4 protein expression, reduced intracellular ROS production, alleviated excessive oxidative stress and inflammatory responses induced by high glucose, and downregulated the expression of adhesion molecules VCAM-1 and ICAM-1. This comprehensive action effectively blocked the progression of diabetic kidney disease at the renal tubular injury level (62).

These studies demonstrate that miR-146a participates in the pathological progression of diabetic kidney disease across multiple dimensions by regulating a variety of downstream functional molecules, establishing it as a potential therapeutic target with significant clinical translational value (37,125,126). Interventional explorations based on this target have also advanced considerably. A study by Aboismaiel *et al* (126) found that 6-gingerol, a natural active component, can upregulate the expression of miR-146a and miR-223, leading to the inhibition of excessive activation of the TLR4/TRAF6/NLR family pyrin domain-containing 3 (NLRP3) inflammasome, thereby exerting a notable renal protective effect in a rat

model of diabetic kidney disease. Moreover, research related to cell therapy has introduced an innovative approach for the clinical translation of this target (127). Human umbilical cord mesenchymal stem cells (UC-MSCs) can release miR-146a-5p through a paracrine pathway, which targets TRAF6 in macrophages, inhibiting the downstream pro-inflammatory STAT1 signaling pathway. This action further induces macrophages to polarize toward the anti-inflammatory M2 phenotype, ultimately leading to a significant reduction in the local renal inflammatory response in rats with diabetic kidney disease (127) (Fig. 5 and Table SII). This study proposes the use of miRNA-modified MSCs as a novel strategy to enhance the efficacy of cell therapy, offering creative avenues for the treatment of diabetic nephropathy.

*Diabetic foot ulcers (DFUs)*. DFUs are typically difficult to heal, with inflammation serving as a core driving factor in their onset and progression (128,129). In addition to regulating the local inflammatory response in the wound and influencing wound healing, the inflammatory regulatory pathway mediated by miR-146a plays a critical role in the pathological processes of diabetic nephropathy. Bi *et al* (130) reported that, compared with wild-type (WT) mice, skin wound healing was significantly delayed in miR-146a knockout (KO) mice. Furthermore, in diabetic mice, wound healing was also delayed, with the most severe delay observed in diabetic miR-146a KO mice (WT > miR-146a KO > diabetic WT > diabetic miR-146a KO) (130). The mRNA and protein levels of IL-1β and TNF-α in the wound tissue were significantly increased in miR-146a KO mice, particularly in diabetic miR-146a KO mice (130). Additionally, expression levels of TRAF6, IRAK1, and NF-κB genes and proteins, as well as key components of the NF-κB signaling pathway, were upregulated in the wound tissues of both miR-146a KO and diabetic mice. These findings suggest that the deficiency of miR-146a delays wound healing by enhancing the NF-κB-mediated inflammatory response (130).

Subsequent research has further refined this regulatory mechanism at the level of immune cell subsets. Macrophages derived from diabetic patients exhibit a distinct characteristic of downregulated miR-146a expression (131). Overexpression of miR-146a was shown to promote M2 macrophage polarization and reduce the release of inflammatory factors, such as IL-6, TNF-α, and inducible nitric oxide synthase (iNOS), by inhibiting the TLR4/NF-κB pathway, thereby accelerating ulcer healing in diabetic mice (131). Investigations of cell delivery strategies based on this mechanism have led to innovative advancements. Exosomes derived from bone marrow mesenchymal stem cells carrying miR-146a-5p (designated as EXO-miR-146a) were found to suppress TRAF6 expression, promote M2 macrophage polarization, ameliorate endothelial inflammation, and restore endothelial function, thus facilitating diabetic wound healing (131) (Fig. 5 and Table SII).

Clinical research has further corroborated the *in vivo* pathological association. In a clinical study involving 90 subjects, participants were divided into three groups: A control group, an uncomplicated T2DM group, and a DFU group (132). The results indicated that patients with grade 2 and 3 DFUs exhibited significantly lower expression levels of miR-146a compared with those with grade 0 and 1 DFUs (132). Inflammatory genes regulated by miR-146a (including TRAF6, IRAK1, and ADAM) were upregulated in patients with both grade 2 and grade 3 DFUs. Reduced levels of miR-146a were associated with increased markers of endoplasmic reticulum stress and oxidative stress in these patients (132). *In vitro* tests demonstrated that miR-146a expression in fibroblasts was downregulated in response to high glucose, endoplasmic reticulum stress, and oxidative stress. It is hypothesized that decreased miR-146a expression is associated with elevated oxidative stress and endoplasmic reticulum stress in more severe cases of DFU. Targeting miR-146a may potentially reduce oxidative and endoplasmic reticulum stress associated with diabetic complications (132). However, the direct causal regulatory mechanisms linking miR-146a to oxidative stress and endoplasmic reticulum stress have yet to be fully elucidated in existing studies.

*Other complications related to diabetes*. Diabetes has been shown to significantly increase the risk of cardiovascular and cerebrovascular complications (133,134). A series of studies has examined the role of miR-146a in diabetic cardiovascular and cerebrovascular injuries, revealing distinct regulatory characteristics of this molecule across different tissues (10,135).

In cardiac research, the expression levels of both miR-146a and NF-κB were found to be significantly elevated in the cardiac tissues of diabetic rats as well as in HUVECs cultured under high-glucose conditions (135). Concurrently, mRNA and protein levels of IRAK1 and TRAF6 in the hearts of diabetic rats were markedly upregulated. Subsequent intervention experiments demonstrated that transfecting high-glucose-treated HUVECs with miR-146a mimics effectively inhibited the abnormal increase in NF-κB activity induced by high glucose (135). Based on these findings, the research team proposed that high glucose initially activates the NF-κB pathway, which subsequently induces the upregulation of miR-146a to initiate physiological negative feedback regulation. However, in the persistent pathological state of diabetes, the compensatory elevation of miR-146a does not result in the downregulation of its target proteins, IRAK1 and TRAF6. This regulatory defect compromises the negative feedback mechanism of miR-146a, ultimately leading to sustained activation of NF-κB and its downstream targets, resulting in pathological abnormalities within cardiomyocytes (135).

In contrast to the compensatory upregulation of miR-146a observed in cardiac tissue, research focusing on diabetic encephalopathy revealed an entirely opposite expression profile (10). In the brain tissue of chronic type 2 diabetic rats, miR-146a expression was significantly reduced, accompanied by elevated levels of inflammatory markers such as cyclooxygenase-2 (COX-2), TNF-α, and IL-1β, alongside increases in oxidative stress markers such as MDA and p22phox. Conversely, the expression of antioxidant proteins, including nuclear factor erythroid 2-related factor 2 (Nrf2), heme oxygenase-1 (HO-1), and SOD, was markedly decreased (10). These findings suggest that miR-146a may serve as a comprehensive negative indicator reflecting the status of inflammation and oxidative stress in the brain tissue of chronic T2DM rats (10). However, the specific underlying molecular mechanisms associated with this phenomenon have yet to be elucidated in existing studies. It is hypothesized that miR-146a may regulate neuroinflammation and oxidative stress by targeting and inhibiting IRAK1

and TRAF6, which are key regulatory factors of the NF-κB pathway; this hypothesis requires further verification in future investigations.

## 5. Delivery system targeting miR-146a

As a multifunctional miRNA, miR-146 plays a critical regulatory role in the onset and progression of various diseases. By modulating the expression levels of miR-146, it can effectively regulate disease-related signaling pathways, thereby achieving therapeutic outcomes (136-139). The development of specific delivery systems is essential for targeted intervention of miR-146, as it can reduce off-target effects and enhance the safety and effectiveness of treatment (90,140,141).

Exosomes, characterized by their natural biocompatibility and low immunogenicity, are capable of crossing physiological barriers such as the blood-brain barrier, making them an ideal natural drug delivery system (140,141). Research conducted by Shafei *et al* (90) demonstrated that exosomes loaded with miR-126/miR-146a significantly enhanced endothelial cell migration and angiogenesis. In animal models, the treatment group exhibited a reduction in infarct size, upregulation of angiogenesis markers such as CD31 and connexin 43, and decreased myocardial fibrosis (90). Additionally, Meng *et al* (142) developed a targeted delivery system using milk exosomes (MEs) for the effective delivery of miR-146a to ischemic myocardium. Their findings revealed that MEs could effectively encapsulate and protect miR-146a, which was subsequently taken up by cardiomyocytes (142). Oral or intravenous administration of MEs-miR-146a improved cardiac function following MIRI and reduced the release of pro-inflammatory factors (TNF-α, IL-1β, and IL-6) and cardiomyocyte apoptosis (142). Further molecular mechanism study indicated that miR-146a exerts anti-inflammatory and anti-apoptotic effects by inhibiting the IRAK1/TRAF6/NF-κB signaling pathway (142).

In addition to exosomal delivery systems, lipid nanocarriers and polymer nanoparticles are also key research directions in current targeted miR-146 delivery approaches (143-145). A study by Bobba *et al* (143) revealed that mechanical ventilation-induced injury upregulates miR-146a in alveolar macrophages as a compensatory response to limit damage; however, the extent of natural upregulation was insufficient to effectively counteract injury (143). Consequently, they designed a lipid nanoparticle loaded with miR-146a, showing that this method effectively regulated the mechanical signal transduction pathway in macrophages, inhibited pro-inflammatory responses, and subsequently reduced ventilator-induced lung injury in mouse models (143). Another investigation employed mannose-modified lipid nanoparticles (MLNP) to target the delivery of miR-146a specifically to alveolar macrophages (144). Results indicated that MLNP-miR-146a treatment significantly lowered pulmonary inflammatory factors, including IL-6 and C-X-C motif chemokine ligand 1 (CXCL1), while improving lung function in mice suffering from acute respiratory distress syndrome induced by hemorrhagic shock (144). Notably, MLNP exhibited no significant *in vivo* toxicity in mice (144). These two studies (143,144) illustrate that targeted delivery of miR-146a to macrophages can effectively alleviate lung inflammation, presenting a promising therapeutic strategy for lung injury.

In the realm of vascular inflammation research, Ho *et al* (145) developed a cationic liposome composed of DPPC/DOTAP/DSPE-PEG/CHOL to encapsulate miR-146a. This liposome exhibited uniform particle size, favorable stability, and high encapsulation efficiency, enabling efficient transfection of target cells (145). Notably, the results demonstrated that this liposome treatment significantly reduced LPS-induced expression of ICAM-1and monocyte adhesion in LPS-stimulated HAECs and aortic SMCs (145). In macrophages, the liposome decreased the expression of TRAF6 and IRAK1, inhibiting the secretion of TNF-α and IL-1β, and reduced oxLDL uptake and foam cell formation. These findings indicate that the liposome can effectively target multiple critical pathways involved in vascular inflammation, positioning it as a promising nanotherapeutic strategy for vascular inflammatory diseases such as atherosclerosis (145). Additionally, Sano *et al* (146) created polyion complex (PIC) micelles loaded with miR-146a-5p and modified with a cyclic arginine-glycine-aspartic acid (cRGD) targeting peptide. Experimental outcomes demonstrated that these targeted PIC micelles effectively localized to damaged blood vessel walls. Following a single administration, the treatment markedly inhibited the expression of pro-inflammatory cytokines [IL-1β and monocyte chemoattractant protein-1 (MCP-1)] in injured rat blood vessels, reduced monocyte/macrophage infiltration and cell proliferation, decreased intimal hyperplasia, and improved vascular remodeling (146). The authors speculated that targeted nanomedicines containing miR-146a-5p could regulate the inflammatory response at the site of vascular injury by inhibiting the NF-κB pathway, although further experiments are necessary to substantiate this hypothesis (146).

In diabetic wound research, Niemiec *et al* (147) utilized a conjugate of cerium oxide nanoparticles carried by nanowire solutions (NS) along with anti-inflammatory miR-146a (CNP-miR146a) to treat skin wounds in diabetic mice. The study found that treatment with a 7% nanofilament solution significantly increased the maximum load and elastic modulus of human diabetic skin (147). Furthermore, the NS + CNP-miR146a treatment resulted in shortened wound healing times in diabetic mice, reduced the expression of pro-inflammatory genes IL-8 and IL-6, and enhanced the expression levels of pro-fibrotic genes TGF-β1, collagen type III α1 chain (Col3a1), and collagen type I α2 chain (Col1a2), as well as collagen levels, compared with the control group (147). This research marks the first application of nanowires as a biomaterial with dual functionalities, encompassing mechanical enhancement and drug delivery, in the treatment of diabetic wounds, proposing a synergistic approach that integrates antioxidant, anti-inflammatory, and mechanical strengthening strategies (147).

Notably, Phạm *et al* (69) developed poly(lactic-co-glycolic acid) (PLGA) nanoparticles (miR-NPs) loaded with miR-146a-5p, which exhibited suitable particle size, zeta potential, and sustained-release properties. Notably, miR-NPs inhibited several inflammatory pathways, including NF-κB and p38 MAPK, and reduced the release of pro-inflammatory cytokines (IL-6, IL-1β, and TNF-α) by targeting spinal cord

microglia. This interaction produced long-lasting analgesic effects in a neuropathic pain model induced by sciatic nerve ligation in rats (69). This study integrates the anti-inflammatory properties of miR-146a-5p with the drug delivery advantages of PLGA nanoparticles, presenting an innovative approach for treating neuropathic pain (69).

These studies illustrate that delivery systems targeting miR-146a can encapsulate or adsorb the miRNA through nanocarriers, exosomes, and other vehicles, thereby protecting it from nuclease degradation and enhancing cellular and tissue uptake (145,148,149). This process amplifies the anti-inflammatory effects of miR-146a, particularly regarding the inhibition of the NF-κB pathway (IRAK1/TRAF6 axis), and facilitates lesion site enrichment and visual monitoring in certain systems (145,148,150). Among these delivery systems, exosomes show considerable potential for the clinical translation of targeted miR-146 therapy. As natural nanovesicles secreted by cells, exosomes possess superior biocompatibility and extremely low immunogenicity compared with artificially synthesized lipid nanoparticles and polymeric nanoparticles, resulting in minimal immune activation even after repeated administration (151,152). Furthermore, their membrane structure closely resembles that of human cell membranes, allowing for efficient passage through various physiological barriers such as the blood-brain barrier and regions affected by myocardial ischemia. This capability enables deep lesion enrichment that is challenging for other artificial carriers to achieve (142,153). The lipid bilayer structure of exosomes effectively encapsulates miR-146, completely preventing nuclease degradation and significantly extending its *in vivo* circulation half-life (90). Moreover, exosomes can be modified with peptides to enhance retention within lesion sites, such as the infarcted heart, thereby markedly improving targeting precision (142).

Although some systems achieve high delivery efficiency in target organs, they often encounter the persistent challenge of 'low arrival rate'. Research indicates that the nano-delivery efficiency to sites such as the heart and aorta typically does not exceed 1% of the injected dose (154). The absence of quantitative distribution data across different cell types (for example macrophages vs. endothelial cells) complicates the evaluation of targeting efficiency (155). Additionally, RNA therapies frequently exhibit issues related to immune activation, which is particularly pronounced in chronic diseases requiring repeated administration (156). For instance, a clinical trial involving a liposomal miR-34a mimic was halted due to significant immune-related adverse events, implying that both the delivery system and the RNA sequence could trigger uncontrollable immune responses (157). Moreover, the multimodal target properties of miRNAs signify that miR-146a can elicit differential biological effects across various cell types, heightening the risk of unintended off-target effects. Lastly, even if nanoparticles are successfully internalized by cells, the active components must escape from endosomes and lysosomes to access the cytoplasm and exert their function. Studies have indicated that only 0.3-2% of N-acetylgalactosamine (GalNAc)-conjugated siRNA achieve endosomal escape, and this process is relatively slow, constituting a critical link that limits overall efficacy (156). The delivery system for miR-146a may encounter similar challenges.

In the context of clinical translation, numerous challenges persist. Exosome-based delivery systems currently lack a standardized separation process, which complicates the precise control of miR-146a loading content during large-scale production. Consequently, the consistency and stability of products across different batches cannot be guaranteed, posing a significant bottleneck for translation efforts. Additionally, most existing studies are confined to short-term animal experiments, lacking comprehensive long-term safety evaluations and pharmacokinetic assessments. Although the pH-responsive gel/mesoporous silica nanoparticle (MSN) system has undergone a 15-day subacute toxicity study without observed abnormalities, quantitative pharmacokinetic parameters, such as nasal mucosal retention half-life and clearance rate, as well as data regarding 90-day long-term toxicity, immunotoxicity, and reproductive toxicity, remain to be addressed (149). Furthermore, the clinical evaluation system is inadequate. In evaluating the therapeutic effects of miR-146 delivery systems, no unified testing standard for biomarkers has been established, hindering accurate quantification of their functional efficiency within the human body and delaying the progress of clinical application submissions.

## 6. Conclusion and future perspectives

Current research continues to explore the specific mechanisms of action of miR-146a in cardiovascular diseases and endocrine and metabolic disorders. Several studies have elucidated the involvement of miR-146a in the pathogenesis of conditions such as atherosclerosis, MI, myocardial fibrosis, and diabetes by regulating key processes including inflammation, immune response, apoptosis, and fibrosis. These insights not only enhance our understanding of the underlying mechanisms of cardiovascular, endocrine, and metabolic diseases but also pave the way for the development of novel therapies targeting these pathological processes. However, miR-146a does not consistently exert a protective effect across all inflammatory diseases and may even induce maladaptive responses under specific conditions. This variability is fundamentally influenced by factors such as disease course, expression dosage, cell type, and the pathological microenvironment.

From the perspective of intrinsic mechanisms, the canonical function of miR-146a involves targeting IRAK1 and TRAF6 to inhibit the NF-κB pathway via negative feedback, thereby suppressing the release of pro-inflammatory cytokines and serving as an 'inflammatory brake' that confers protective effects during short-term acute inflammation (158). However, this protective effect operates within strict boundaries. The first factor influencing this boundary is the variability in disease course. For instance, transient upregulation of miR-146a under short-term high-glucose conditions can effectively control inflammation (43). By contrast, sustained high expression of miR-146a during long-term chronic inflammation (159,160) may excessively inhibit immune clearance, cellular repair, and antioxidant pathways, preventing the anti-inflammatory benefits from offsetting persistent tissue damage (161,162). Secondly, a dosage window exists where moderate upregulation of miR-146a inhibits excessive inflammation, whereas excessive and prolonged expression can interfere with genes associated with cellular homeostasis, leading to injury (163,164). For

example, excessive miR-146a in cardiomyocytes was shown to inhibit the calcium transporter sarcoplasmic/endoplasmic reticulum $Ca^{2+}$-ATPase 2a (SERCA2a) and small ubiquitin-like modifier 1 (SUMO1), thereby inducing cardiac hypertrophy and dysfunction (163). Similarly, high concentrations of miR-146a in the intestine were found to downregulate tight junction proteins, compromise the intestinal mucosal barrier, and shift its role from an anti-inflammatory factor to an injury mediator (164). Thirdly, the effects of miR-146a are highly cell-type specific. In immune cells such as macrophages and monocytes, the primary targets of miR-146a are IRAK1 and TRAF6, which primarily confer anti-inflammatory functions (83). Conversely, in neurons, cardiomyocytes, and intestinal epithelial cells, miR-146a not only targets inflammatory genes but also regulates genes involved in cell survival, nerve regeneration, calcium homeostasis, and anti-senescence processes (165-167). Although upregulated miR-146a controls inflammation in immune cells (83), it can directly promote apoptosis and fibrosis in neurons and cardiomyocytes (166). Lastly, pathological microenvironments, such as those characterized by hyperglycemia and oxidative stress in diabetes, disrupt the negative feedback loop associated with miR-146a, thereby diminishing its anti-inflammatory effects (132). Consequently, while the body may upregulate miR-146a in a compensatory manner to resist injury, long-term accumulation can exacerbate lesions and lead to a vicious cycle. It can be concluded that miR-146a does not possess an absolute 'beneficial/harmful' attribute but functions as a dynamic feedback regulator of inflammation: Short-term, moderate upregulation primarily acting on immune cells is protective, while chronic, sustained, excessive upregulation that broadly influences parenchymal cells becomes maladaptive and pathogenic.

Despite progress in the field, numerous challenges remain to be addressed. First, the specific regulatory network of miR-146a in various diseases and across different pathological stages has not been fully elucidated. Second, further optimization is required regarding the targeting efficiency, biological safety, and stability of large-scale preparations of different vectors. Third, the translation of therapies targeting miR-146a to clinical application is still a significant distance away from realization. Future research should primarily focus on three key aspects: First, enhancing the understanding of the regulatory network of miR-146a across various diseases and stages of disease progression should be a priority. Multi-omics integrated technologies, including transcriptomics, proteomics, and epigenomics, could be utilized to compare samples from different stages, such as acute vs. chronic inflammation and painless vs. painful diabetic neuropathy. This approach aims to systematically identify the upstream and downstream target genes and transcription factors associated with miR-146a. Additionally, cellular and animal gene-editing models should be developed to enable segmented knockout and overexpression of miR-146a, facilitating the differentiation of its specific pathways in immune and nerve cells. Second, efforts should be directed toward optimizing the efficiency, safety, and mass production processes of targeted delivery vectors. A comparative analysis would assess the advantages and disadvantages of lipid nanoparticles, exosomes, peptide vectors, and viral vectors, with a particular emphasis on developing engineered exosomes derived from mesenchymal stem cells that possess low immunogenicity and modifications for nerve targeting. Moreover, standardized and large-scale protocols for low-temperature preparation, purification, and quality control should be established, with optimized storage conditions to resolve issues related to batch stability and high production costs. Improvements to the *in vivo* degradation profiles and long-term safety evaluation systems of these vectors should also be pursued. Third, to expedite the clinical translation of miR-146a-targeted therapy, small-sample prospective cohort studies should be conducted to validate miR-146a as a prognostic biomarker, facilitating non-invasive risk stratification. Subsequently, stepwise interventional animal experiments may be designed to differentiate the therapeutic effects of short-term low-dose administration vs. long-term high-dose administration, thereby identifying the safe and effective administration window. Exploration of synergistic treatment regimens that combine miR preparations with hypoglycemic and antioxidant drugs should be conducted, alongside the establishment of a standardized framework for administration and therapeutic effect evaluation to promote clinical implementation.

With the ongoing advancements in molecular biology and nano-delivery technology, there is a strong belief that the mechanisms of miR-146a in inflammation-related diseases can be further clarified. The development of safer and more efficient targeted delivery systems holds promise for bringing related treatment options into clinical practice, ultimately offering new therapeutic hope for patients suffering from a variety of inflammation-related diseases.

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**Authors' contributions**

XY contributed to designing the scope and structure of the review, and wrote major sections of the manuscript. PL performed structured literature searches. HZ acquired the funding, and critically synthesized and interpreted the findings. All authors read and approved the final manuscript. Data authentication is not applicable.

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## Competing interests

The authors declare that they have no competing interests.

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