Mechanisms and application strategies of miRNA-146a regulating inflammation and fibrosis at molecular and cellular levels (Review)

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Abstract. In the progression of various diseases, inflammation has a critical role. Chronic persistent inflammation is a pivotal trigger of fibrosis. Several microRNAs (miRNAs) participate in inflammation and fibrosis. In recent years, it has been proved that miRNAs are a critical link in physiological and pathological processes. Among them, the miRNA miR-146a has a pivotal role in the immune system and acquired immunity, making it one of the most studied miRNAs. Due to its essential roles at the molecular and cellular levels, it has broad application prospects in precision medicine. The present comprehensive review focused on the mechanisms of miR-146a and its application strategies in inflammation and fibrosis, discussing its therapeutic potential. The main signaling pathways through which miR-146a regulates inflammation and fibrosis and their relationships were covered. Furthermore, the functions and effects of miR-146a in specific cells, which may join in the process of inflammation and fibrosis, were outlined. Application strategies were also summarized according to recent studies based on these mechanisms.

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Abbreviations: EMT, epithelial-mesenchymal transition; α-SMA, smooth muscle α-actin; miRNA, microRNA; RISC, RNA-induced silencing complex; 3'UTR, 3'-untranslated region; IRAK1, interleukin-1 receptor-associated kinase 1; TRAF6, tumor necrosis factor receptor-associated factor 6; STAT, signal transducers and activators of transcription; NF-κB, nuclear factor-κB; JAK, Janus kinase; KEGG, Kyoto Encyclopedia of Genes and Genomes; GO, Gene Ontology; FOXP3, forkhead box protein 3; IL-1R, IL-1 receptor; TLR, Toll-like receptor; LPS, lipopolysaccharide; H3K27me3, tri-methylation at lysine 27 of histone H3; ETS-1, V-Ets oncogene homolog 1; TIR, Toll/IL-1 receptor; MYD88, myeloid differentiation factor 88; TRIF, TIR domain-containing adaptor molecule; IκBα, inhibitor of kappa Bα; HSC, hepatic stellate cell; Th1, type 1 T helper cell; Treg, regulatory T cell; MHCII, major histocompatibility complex class II; lncRNA, long non-coding RNA; DC, dendritic cell; NK, natural killer; TGF-β, transforming growth factor-β; ECM, extracellular matrix; Col-1, collagen 1; Smad, Small mothers against decapentaplegic; R-smad, receptor-mediated Smad; VIM, vimentin; Bambi, BMP and endogenous bait receptors for activin membrane-binding inhibitors; EZH2, enhancer of zeste homolog 2

Key words: miR-146a, inflammation, immune cells, fibrosis, biomarker, treatment

Contents

1. Introduction

Inflammation and fibrosis are inseparable from disease. Organ fibrosis is frequently induced by persistent chronic inflammation triggered by several stimuli, although it may have multiple causes (1). Type 2 T helper (Th2) cells have strong profibrotic capacities and induce M2-type expression of macrophages. Macrophages have essential effects on inflammation and fibrosis via several pathways (2,3). Chronic inflammation and epithelial-mesenchymal transition (EMT) create a profibrotic environment that promotes the production of collagen and smooth muscle α-actin (α-SMA) by infiltrating hematopoietic cells and resident fibroblasts. Several interactions among fibroblasts, fibrocytes and inflammatory cells also attenuate or exacerbate fibrosis (4).

MicroRNAs (miRNAs) mediate several functions in cells. They are pivotal regulators in cellular pathways and numerous pathologies, although they do not code for proteins. With RNA-polymerase II/III catalyst, miRNAs encoding genes are transcribed into primary miRNAs. The primary miRNAs are cleaved with Drosha (the first RNase III enzyme)

into precursor miRNAs of ~60-70 nucleotides in the nucleus, and exportin-5 transports these precursor miRNAs into the cytoplasm. Subsequently, the second RNase III enzyme, Dicer, cleaves them into ~22-nucleotide double-stranded miRNA molecules (5). The RNA-induced silencing complex (RISC) incorporates the mature miRNAs, in which they further perform their functions. Finally, these miRNAs bind to the 3'-untranslated regions (3'UTRs) of the target genes and degenerate or reduce mRNA expression (6). miRNAs mediate mRNA degradation mainly by deadenylation, subsequent decapping and 5'-3' exonucleolytic digestion (7).

In a physiological environment, the expression of miR-146a is confined to immune cells, and it negatively inhibits the innate and adaptive immune responses by regulating certain adapters or transcription factors, including signal transducer and activator of transcription 1 (STAT1) (8,9), tumor necrosis factor receptor-associated factor 6 (TRAF6) and interleukin-1 receptor-associated kinase 1 (IRAK1) (10-13). Fig. 1 illustrates the biological functions and top 30 enriched pathways of miR-146a-5p from the Gene Ontology and Kyoto Encyclopedia of Genes and Genomes enrichment analysis [the results were obtained from the CancerMIRNome database (http://bioinfo.jialab-ucr.org/CancerMIRNome/)]. The nuclear factor-κB (NF-κB) signaling pathway and Toll-like receptor (TLR) are related to inflammation. Binding cytokine receptor is also an inflammation-related biological function. The present review focused on describing the mechanisms and application strategies of miRNA-146a in regulating inflammation and fibrosis at molecular and cellular levels.

2. Location and transcription regulation of miR-146a

The miR-146 family (miR-146a and miR-146b) are homologous, with only two nucleotides differing in their 3' region. Their coding genes are located on 10 (10q24.32) and chromosomes 5 (5q33.3) in humans (14). These isoforms have similarities and differences in function and target molecules. They have unique regulatory functions for the signaling pathway (15,16). The miR-146a precursor contains a 5' arm sequence (miR-146a-5p) and a 3' arm sequence (miR-146a-3p). miR-146a is the main topic of the present review. The gene motif's binding promoter of miR-146a reported in studies on inflammation or fibrosis will be discussed. Liu *et al* (17) found two pairs of NF-κB binding motifs (GGGATTTCC and GGGACTTTCC in humans) and forkhead box protein 3 (FOXP3) binding motifs (GCCAACA and GCAAATA in humans) in the miR-146a promoter. NF-κB is a pivotal factor in inflammation and fibrosis, while FOXP3 is the transcription factor of T-regulatory (Treg) cells and participants in immune responses. IL-1 receptors (IL-1R)/TLRs stimuli, such as lipopolysaccharide (LPS) and NF-κB signaling, lead to its expression. The expression of miR-146a downregulates the activity of these pathways (14,15,18). In rats with acute spinal cord injury, Ni *et al* (19) found that tri-methylation recruitment at lysine 27 of histone H3 (H3K27me3) around the upstream region in the promoter of miR-146a reduced miR-146 expression, suggesting that H3K27me3 participates in the epigenetic regulation of miR-146a. By interfering with the maturation process of miRNA, genetic variants in miRNA precursors affect miRNA expression levels and thereby cause disease susceptibility. These variants may occur in the miRNA promoter and precursor regions. Single nucleotide polymorphisms (SNPs) are essential. As a result of the rs2910164 polymorphism, the pre-miR-146a's stem region is mismatched, which indirectly influences the expression of mature miR-146a (20). G:U in rs2910164 changes to C:U, causing mispairing in miR-146a's hairpin and decreasing the efficiency of processing miRNA precursors into mature miRNA, thus suppressing the expression of miR-146a (21). V-Ets oncogene homolog 1 (Ets-1) is a member of the Ets family of transcription factors that activates the miR-146a promoter and directly regulates miR-146a expression. The inflammation risk-associated G allele of rs57095329 inhibits the binding affinity for Ets-1 and leads to an inappropriate compositional change, and is thus another genetic factor suppressing miR-146a expression (22). These two SNPs were in a strong linkage disequilibrium. Cui *et al* (23) found that the miRNA-146a rs57095329 A allele carried a lower risk and seizure frequency of drug-resistant epilepsy (Fig. 2).

3. miR-146a and inflammation

Inhibition of inflammation via the IL-1R/TLRs-NF-κB axis. It is thought that downstream of these receptors are similar signaling cascades, as TLRs and IL-1R both express Toll/IL-1 receptor (TIR) domains (24). The current understanding of TLR signaling is primarily based on studies focusing on downstream IL-1R signaling. TLR2 is involved in peptidoglycan, lipoteichoic acid (LTA) and bacterial lipoprotein metabolism. The stimuli of TLR4 contain LPS, LTA and oxidized low-density lipoprotein (25,26). TLRs transduce downstream signals by mediating the myeloid differentiation factor 88 (MyD88) or TIR domain-containing adapter molecule (TRIF)-related pathways. The binding of IRAK4 and IRAK1/2 are induced to form the myddosome when MyD88 recruits to the TIR domain of TLRs. TRAF6 further activates downstream of MyD88 and triggers NF-κB signaling, inducing pro-inflammatory responses. TRAF6 also induces endosomal TLR4, which is related to TRIF and contributes to pro-inflammatory responses (27). Activated inhibitor κ kinase β induces the phosphorylation of inhibitor of κBα (IκBα), leading to the ubiquitination and subsequent degradation of IκBα, which promotes the release of NF-κB dimers from the cytoplasm to the nucleus (28-30). The canonical NFκB pathway regulates the production of proinflammatory cytokines, growth factors, chemokines, matrix metalloproteinase, antiapoptotic proteins, proinflammatory enzymes, intercellular adhesion molecule 1 and inhibitors of NFκB signaling (such as IκBα) (31,32).

The IL-1R/TLRs-NF-κB signaling pathway functions mainly by targeting IRAK1 and TRAF6. Numerous studies have reported that miR-146a reduced gene expression of IRAK1 and TRAF6 (33-36). In a study of kidney ischemia/reperfusion injury, Li *et al* (37) found that miR-146a downregulated the expression of IRAK1 through binding to its 3'UTR and ultimately inactivated NF-κB, inhibiting the infiltration of inflammatory cells and protecting kidney functions. Another study reported that miR-146a targeted the 3'UTR of TRAF6 and induced LPS-TLR4-NF-κB pathway inhibition, reducing inflammatory mediators such as IL6 and TNF-α (38). Zhang *et al* (39) reported that the 3'UTR of TRAF6 and IRAK1

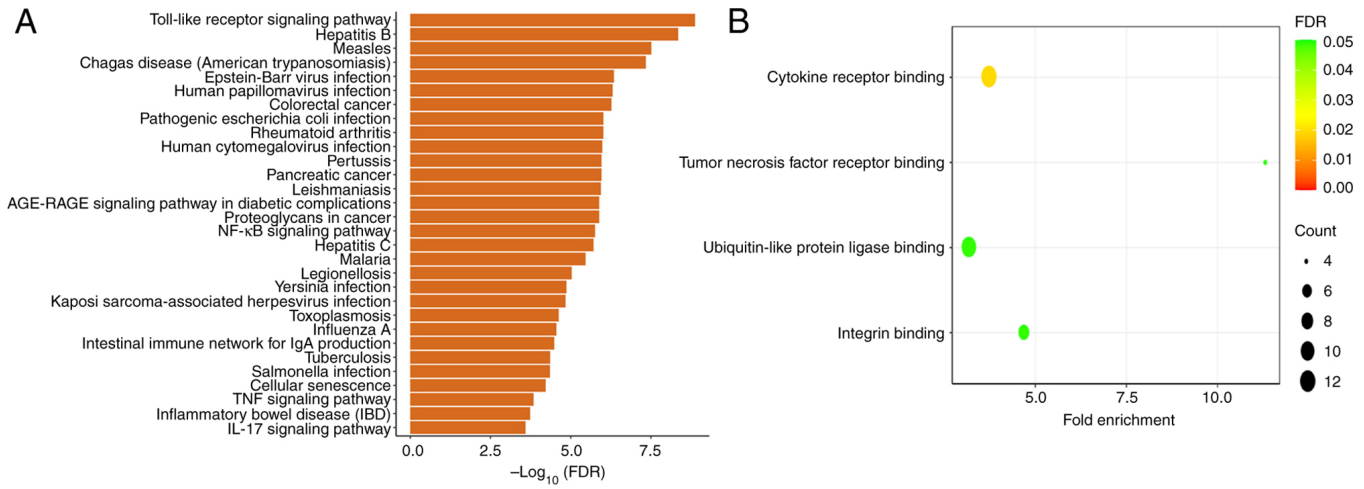

Figure 1. KEGG and GO analyses of signaling pathways and biological functions of miR-146a-5p. (A) Signaling pathways related to miR-146a-5p using KEGG analysis. (B) Biological functions related to miR-146a-5p by GO analysis. The results are obtained from the CancerMIRNome database (http://bioinfo.jialab-ucr.org/CancerMIRNome/). KEGG, Kyoto Encyclopedia of Genes and Genomes; GO, Gene Ontology; miR, microRNA; FDR, false discovery rate.

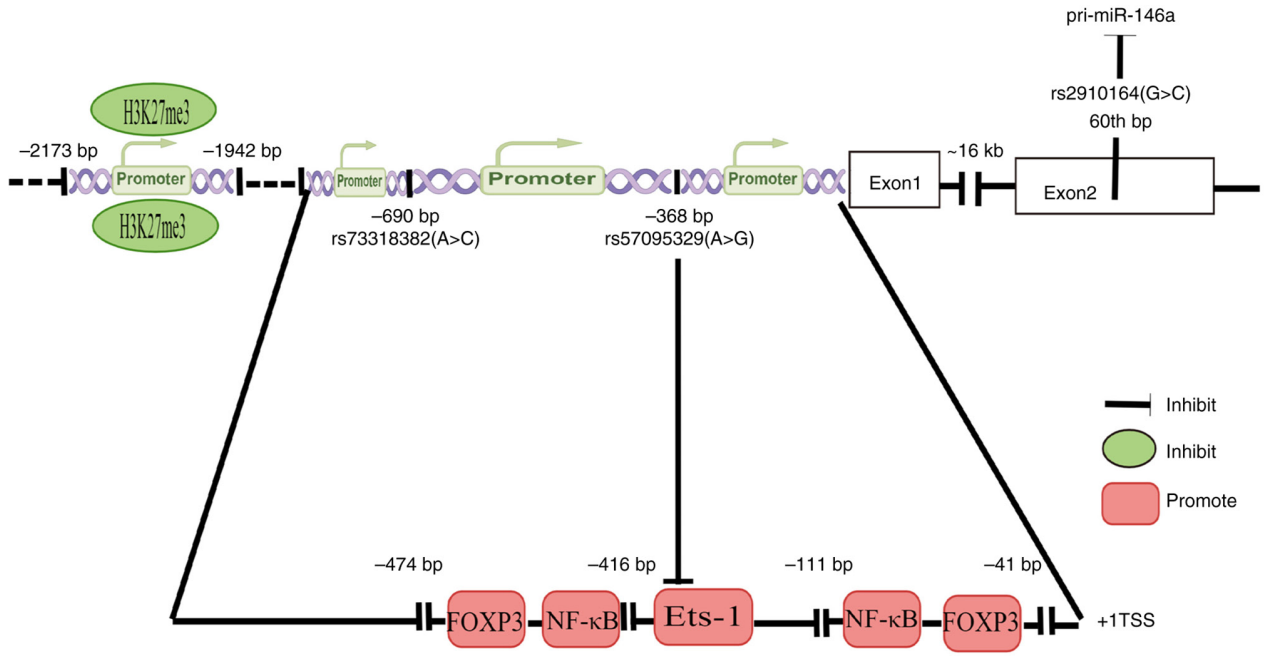

Figure 2. Schematic of miR-146a regulation. The miR-146a polymorphism rs2910164 is located at the 60th nucleotide position in the seed region of pri-miR-146a on chromosome 5q33.3, while rs57095329 and rs73318382 are in the promoter region at -386 and -690 bp, respectively. H3K27me3 recruitments are in the upstream promoter region of miR-146a, from -2,173 to -1942 bp. Two pairs of FOXP3 and NF-κB are located from -474 to -416 bp and -111 to -41 bp, respectively. The figure was drawn with Figdraw (https://www.figdraw.com). miR, microRNA; FOXP, forkhead box protein; ETS-1, Ets oncogene homolog 1; H3K27me3, tri-methylation at lysine 27 of histone H3; TSS, transcription start site.

had binding domains for miR-146a. The release of inflammatory cytokines was decreased by the upregulation of miR-146a, blunting IL-1R1/TLR4 (40). When TLR2 of THP-1 cells was stimulated by bacterial lipoprotein, Quinn *et al* (41) found that overexpression of miR-146a reduced TNF-α expression. When they used LPS to stimulate TLR4 of the human hepatic stellate cell (HSC) line LX2, Chen *et al* (42) found that inflammatory responses and fibrogenesis were inhibited by the overexpression of miR-146a. During inflammation, with the overactivation of the NF-κB pathway, the expression and activity of miR-146a in immune cells led to the downregulation of IRAK1 and TRAF6 genes, finally decreasing the expression of NF-κB transcription factors, particularly inflammatory cytokines. In mice, acute and chronic inflammatory autoimmune responses were overactive in miR-146a-deficient T cells (43). Certain studies reported worsening inflammation in several diseases associated with deficiency of miR-146a (44-46). miR-146a treatment of experimental autoimmune anterior uveitis resulted in significant variations in cytokine production. Pro-inflammatory cytokines were inhibited, such as IL-1β, IL-6 and IFN-γ, while anti-inflammatory cytokines such as IL-10 increased (47). Lv *et al* (48) found that overexpression of miR-146a inhibited TRAF6/NF-κB activation in LPS-induced nucleus pulposus cells. Furthermore, when miR-146a was

deficient in injured mice, inflammation at the wound site deteriorated due to dysregulation of pro-inflammatory cytokines, IRAK1 and TRAF6 (49). These findings suggest that miR-146a attenuates inflammatory responses by targeting the upstream IRAK1 and TRAF6 of NF-κB, the center of the IL-1R/TLRs signaling pathway.

Inhibition of inflammation via the Janus kinase (JAK)-STAT axis. Tang *et al* (50) identified that upregulation of miR-146a decreased the expression of the STAT1 genes, thereby controlling human lupus erythematosus through the IFN pathway. He *et al* (51) demonstrated that hepatic schistosomiasis increased the expression of miR-146a/b in macrophages. IFN-γ inducing macrophages to differentiate into M1 macrophages was reduced by upregulated miR-146a targeting STAT1, presumably as a mechanism of it inhibiting the pro-inflammatory function of M1 macrophages (51). miR-146a regulated the IFN-γ-dependent Th1 cell-mediated spontaneous immunopathology and reduced Treg cell trans-differentiation into Th1 cells by controlling the overactivation of STAT1 in Treg cells (8).

STAT3 is involved in retinal endothelial inflammation in type 1 diabetes and high glucose-induced endoplasmic reticulum stress (52). Elevated STAT3 phosphorylation led to increased production of inflammatory cytokines from macrophages (53). Ocular JAK/STAT3 signaling is activated by IL-6 (54-56), while miR-146a inhibits IL-6. Ye and Steinle (57) reported that miR-146a inhibited inflammation and apoptosis as a potential molecular treatment in the diabetic retina by participating in inhibiting the IL-6-related JAK/STAT3 pathway. Furthermore, miR-146a was reported to inhibit the pro-inflammatory function of STAT3 by targeting homeodomain-interacting protein kinases 3 (58). Downregulation of miR-146a increased the levels of phosphorylated STAT3 protein (59), consistent with the result that STAT3 had significantly higher activity in miR-146a-deficient mice (60). A western blot study by Sun *et al* (61) also demonstrated that miRNA-146a-5p inhibited the activation of STAT3. miR-146a is also involved in inflammation-related Treg/Th17 differentiation by targeting STAT1/STAT3, which will be introduced in the next section.

miR-146a is involved in inflammation by regulating immune cells

Regulation of macrophages. To be consistent regarding Th1 and Th2 differentiation paradigms for T cells, macrophage differentiation involved in the production of various phenotypes was divided into canonical M1 polarization and alternative M2 polarization. M1 macrophages are predominantly pro-inflammatory (62,63). The enhanced expressions of cell-surface activation factors, such as major histocompatibility complex class II (MHCII), CD80 and CD86, and the production of pro-inflammatory factors are the main characteristics involved in antigen presentation functions for M1 activation. M2 macrophages have numerous functions, including inhibiting inflammation and promoting tissue repair (64-67). Peng *et al* (68) demonstrated miR-146a-induced M2 polarization through TLR4/NF-κB to attenuate inflammation and repair wounds in mice with diabetic ulcers. miR-146a has also been found to be involved in inhibiting M1 macrophage polarization (69,70). Huang *et al* (70) demonstrated that the overexpression of miR-146a in M1 macrophages significantly reduced the expression of pro-inflammatory cytokines; on the contrary, miR-146a inhibition promoted the polarization of M1 macrophages. miR-146a inhibits M1 pro-inflammatory responses and miR-146a-deficient diabetic mice exhibited increased M1 and weakened M2 responses, aggravating renal injury (45). Overexpression of miR-146a improved LPS-induced inflammatory responses in macrophages of older mice (71). Macrophage maturation was downregulated by miR-146a through decreased expression of CD80 and CD86, attenuating inflammation (72). miR-146a inhibited M1 polarization and induced M2 polarization by regulating NLRP3 (73) and NOTCH1 (74). The inflammatory inhibition of miR-146a by regulating macrophage polarization was also identified in other studies. By sponging miR-146a, long non-coding RNAs (lncRNAs) such as lncRNA CHRF and lncRNA HCG18 induced M1 polarization and inflammatory responses (75,76).

Regulation of the Th17/Treg balance. Studies indicated that the expression of miR-146a increased in Treg cells (77,78). miR-146a-deficient mice had an elevated percentage of FOXP3-CD4+ T cells and IFN-γ-dependent Th1 pro-inflammatory responses increased in miR-146a-deficient mice through activating STAT1 (target of miR-146) (8). However, one study reported that in patients with allergic rhinitis, miR-146a elevated Treg functions and differentiation via targeting STAT5b (79). Guo *et al* (58) indicated that miR-146a mediated Treg-cell differentiation via upregulating FOXP3 expression. IL-6-driven STAT3 signaling is required for the nuclear retinoic acid receptor-related orphan receptor-γ-t function involved in Th17-cell differentiation. Li *et al* (80) reported that experimental autoimmune encephalomyelitis deteriorated and the differentiation into Th17 cells increased in miR-146a knock-out 2D2 T cells. miR-146a reduced the production of IL-6 and IL-21 in 2D2 T cells, reducing their Th17 differentiation via the STAT3 signaling pathway (80). One study further reported that the inhibition of miR-146a elevated the expression of the NF-κB, STAT3 and TRAF6 genes, leading to the production of pro-inflammatory cytokines such as IL-6, IL-17A and IL-21, which mediated Th17-cell differentiation (59). In oral lichen planus, one group reported that FOXP3 reduced the expression of downstream TRAF6 and promoted CD4+ T-cell differentiation into Treg cells by regulating miR-146a, thereby alleviating chronic inflammation (81). They further indicated that lncRNA DQ786243 overexpression significantly enhanced the expression of miR-146a by targeting FOXP3, thereby suppressing the NF-κB pathway (82).

Regulation of dendritic cell (DC) functions. DC maturation is characterized by the upregulation of the surface antigens CD80 and CD86 (83). It has been reported that miR-146a mimics contributed to immature DC, inducing Treg differentiation and reducing the expression of CD80 and CD86 in the DC surface via the Notch-1 signal pathway. By contrast, miR-146a inhibition had the opposite effect (84). miR-146a appears to be involved in DC tolerogenic properties based on these findings. A study reported that miR-146a overexpression inhibited DC maturation and antigen presentation (85). Through targeting the JAK/STAT1 signaling pathway, miR-146a was indicated to downregulate the expression of MHCII and activation of DCs and decrease the production of inflammatory factors (86).

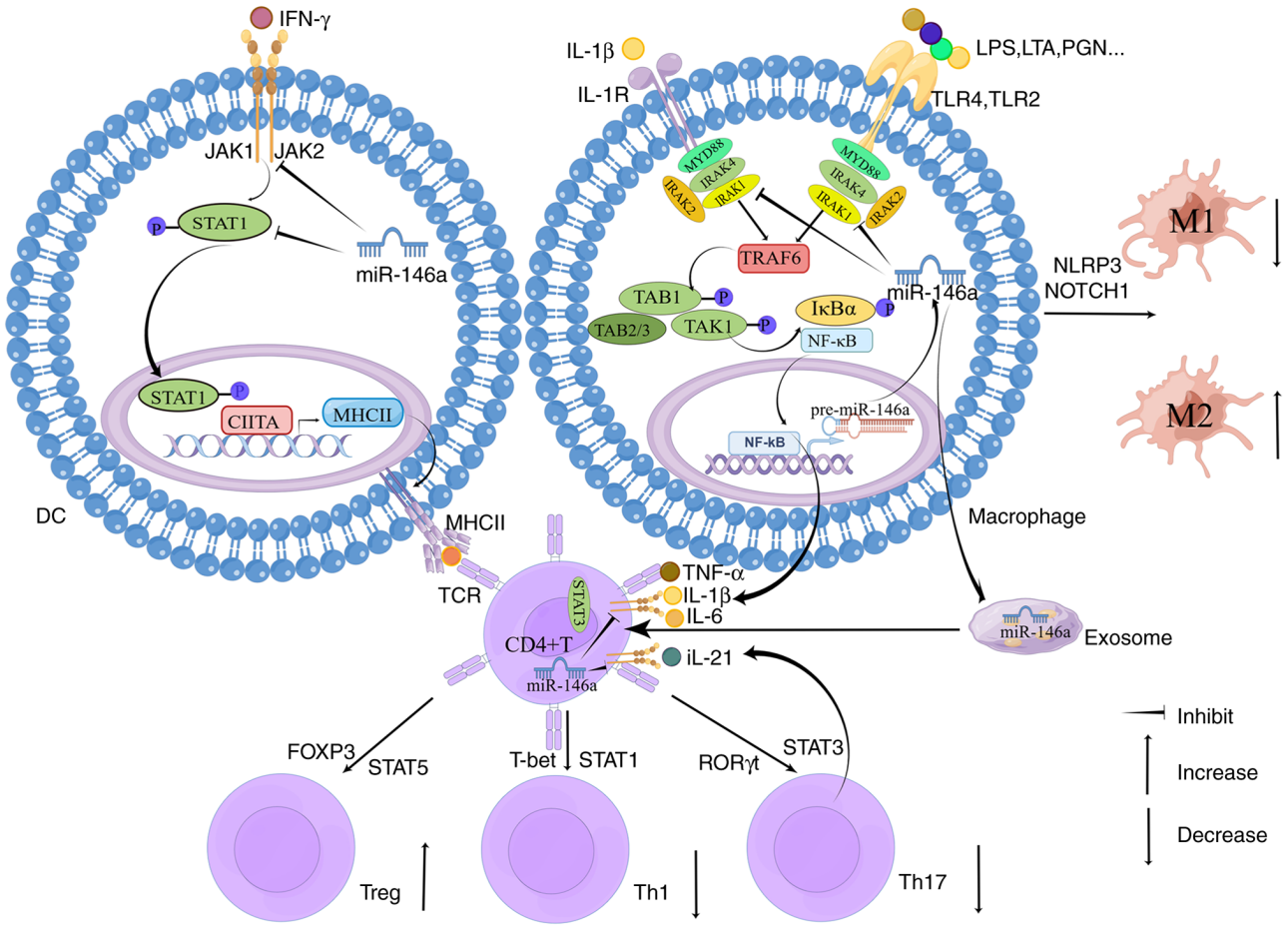

Figure 3. MiR-146a regulates inflammation. MiR-146a is critical in producing inflammatory cytokines and differentiating immune cells, such as CD+ T cells, DCs and macrophages. In DCs, miR-146a inhibits the expression of MHCII through the JAK/STAT1 signaling pathway, and the expression of CD80 and CD86 is also reduced, which impacts the maturation and antigen presentation function of DCs. By contrast, miR-146a suppresses the production of inflammatory cytokines of macrophages by promoting its M2 polarization and targeting the NF-κB signaling pathway. Finally, for the decrease of stimuli from antigen-presenting cells and the functions of miR-146a through different signaling pathways (such as the inhibition of JAK-STAT1/3 and the promotion of STAT5), CD4+ T cells increase anti-inflammatory Treg cell differentiation and decrease pro-inflammatory Th17 and Th1 differentiation. The figure was drawn with Figdraw (https://www.figdraw.com). miR, microRNA; Th1, type 1 T-helper cell; MHC, major histocompatibility complex; DC, dendritic cell; Treg cell, T-regulatory cell; TLR, Toll-like receptor; FOXP, forkhead box protein; LPS, lipopolysaccharide; PGN; peptidoglycan; LTA, lipoteichoic acid; IRAK1, interleukin-1 receptor-associated kinase 1; TRAF6, tumor necrosis factor receptor-associated factor 6; STAT, signal transducers and activators of transcription; NF-κB, nuclear factor-κB; JAK, Janus kinase; MYD88, myeloid differentiation factor 88; NLRP3, NACHT, LRR and PYD domain-containing protein 3; RORγ, retinoic acid receptor-related orphan receptor γ; CIITA, MHCII transactivator; TAK1, TGF-β-activated kinase 1; TAB, TAK-binding proteins; TCR, T-cell receptor.

These findings are consistent with another study (87). miR-146a expression in human plasmacytoid DCs reduced their ability to mediate the proliferation of CD4+ T-cell proliferation by downregulating costimulatory molecules and MHCII on its surface (88). Park *et al* (89) demonstrated that miR-146a overexpression in mature DCs decreased cytokine production and enhanced DC apoptosis by targeting IRAK1 and TRAF6. These studies indicate that upregulation of miR-146a suppresses the activation, maturation and antigen presentation function of DCs via several signaling pathways, and miR-146a may mediate Treg differentiation via DCs.

Regulation of natural killer (NK)-cell functions. Xu *et al* (90) indicated that overexpression of miR-146a reduced the cytotoxic effect induced by NK cells and produced pro-inflammatory cytokines by targeting STAT1. They reported that anti-inflammatory factors transforming growth factor-β (TGF-β) and IL-10 induced the expression of miR-146a (90). Pesce *et al* (91) demonstrated that miR-146a regulated NK cell-mediated cytotoxicity via targeting killer Ig-like receptors. They reported that miR-146a downregulated the levels of IFN-γ in human NK cells and prevented NK cells from becoming over-activated and overproducing IFN-γ by targeting IRAK1 and TRAF6 (92). There are relatively limited studies on the relationship of miR-146a with NK cells, particularly in inflammation. These studies suggested that miR-146a may negatively regulate inflammation through participating in NK-cell functions (Fig. 3).

4. miR-146a and fibrosis

Approximately 45-50% of deaths may be ascribed to fibrosis in developed countries (1,93). Excessive extracellular matrix (ECM) production is a feature of fibrosis and excessive matrix shrinkage in various organs (94). Fibrosis is primarily caused by chronic inflammation mediated by several stimuli (1). In fibrosis models,

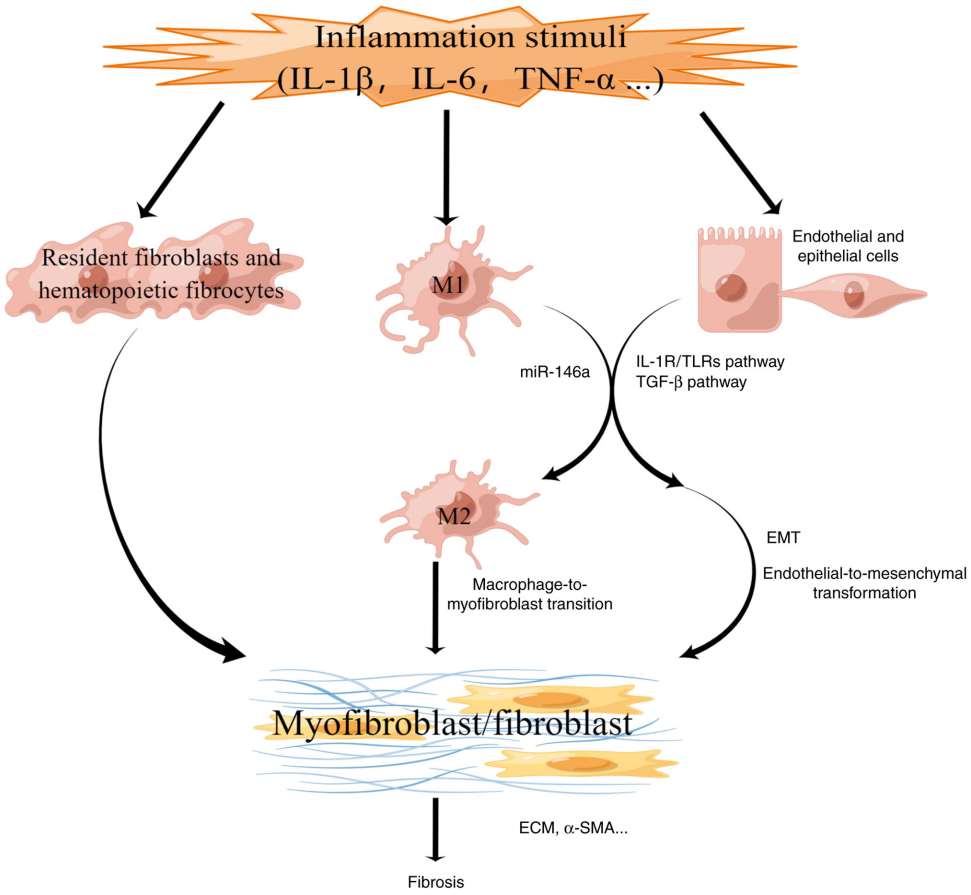

Figure 4. Relationship between inflammation and fibrosis. When inflammation (particularly chronic inflammation) arises, its stimulus signals stimulate resident mesenchymal fibroblasts, and hematopoietic fibrocytes produce ECM. Inflammatory signals lead to M1-type expression by macrophages. MiR-146a and the corresponding IL-1R/TLRs and TGF-β signals promote M1-type macrophages and endothelial and epithelial cells to transform into myofibroblasts. Finally, these myofibroblasts and fibroblasts secrete ECM and α-SMA that induces fibrosis. The figure was drawn with Figdraw (https://www.figdraw.com). ECM, extracellular matrix; SMA, smooth muscle actin; TLR, Toll-like receptor; miR, microRNA.

epithelial cells trans-differentiate into myofibroblasts via EMT activated by chronic inflammation (95). Myofibroblasts produce ECM in the progression of physiological tissue repair and organ fibrosis. Myofibroblasts are derived from endothelial cells, epithelial cells, fixed fibroblasts, smooth muscle cells, pericytes, bone marrow-derived progenitor cell lines and bone marrow-derived fibroblasts (96). The deposition of connective tissue components leads to increased stiffness in the affected tissue and impairs the diffusion of oxygen and nutrients, further inducing sustained myofibroblast activation and cell damage (97-99). Epigenetic modifications induced by profibrotic environments shield myofibroblasts from external stimuli, forming a malignant expansion loop (100,101). Due to the profibrotic effect of excessive fibrosis, TGF-β and other signaling pathways trigger further fibrosis, culminating in organ failure and dysfunction (102).

miR-146a is a pivotal antifibrotic miRNA in numerous tissues (103,104). Studies highlighted the possibility of treating fibrosis by interfering with miR-146 (105,106). Downregulation of miR-146a-5p was found in cirrhotic livers of CCl_4-treated rats and upregulation of miR-146a suppressed the profibrotic function of TGF-β by targeting downstream TGF-β signaling (107). Src kinase inhibitor significantly attenuated the progression of skin and lung fibrosis in mice (108,109). miR-146a overexpression reduced the production of α-SMA and collagen 1 (Col-1) in TGF-β-treated human HSCs by inhibiting Src synthesis (110). It was found that miR-146 expression was downregulated in a fibrotic mouse model after acute muscle injury and overexpression of miR-146a attenuated the secretion of ECM *in vitro* and *in vivo* (111). Liu *et al* (112) reported that miR-146a reduced the production of Col-1 and hyaluronic acid of ECM in orbital fibroblasts. After induction of ischemia/reperfusion injury, tubular injury, inflammatory infiltrates and fibrosis worsened in miR-146a-deficient mice as compared to wild-type mice (113). miR-146a suppressed myocardial fibrosis by targeting the TRAF6 and IRAK1 genes by targeting the TLR-4-NF-κB pathway (114).

These studies indicate that miR-146a regulates the fibrosis process inside cells through signaling pathways, which are classified into two types in the present review (Fig. 4). In addition, it is also necessary to explore the functions of miR-146a at the level of fibrosis-related cells in the future.

Main signaling pathways of miR-146a

Small mothers against decapentaplegic (Smad)-dependent TGF-β signaling pathway. The TGF-β signaling pathway regulates adaptive and innate immunity, fibrosis and inflammation (115). TGF-β switching accelerated the development or progression of fibrosis in chronic inflammatory autoimmune conditions (116,117). The activation of fibrotic factors produced by inflammatory and epithelial cells was observed during the

progression of chronic autoimmune diseases. Organ fibrosis is characterized by sustained fibroblast proliferation and inflammation (118). TGF-β1 treatment of HSCs led to elevated expression of α-SMA and Col-1 and decreased expression of miR-146a-5p (119). Overexpression of miR-146a reduced the levels of α-SMA and Col-1 in TGF-β-treated HSCs (110).

The primary signaling pathway mediated by TGF-β involves the phosphorylation of Smad2/3 protein to form receptor-mediated Smad/co-regulated Smad4 complex (120). This Smad complex accumulates in the nucleus and triggers the transcription of target genes (e.g., SNAIL) by activating transcription factors (121) and mediating signaling events associated with EMT activation. SNAIL is involved in the downregulation of E-cadherin and claudins, upregulating vimentin (VIM) and fibronectin (122). The induction of EMT markers and SNAIL activation led to upregulation of the ECM markers Col-1 and VIM and the suppression of the epithelial marker E-cadherin. Several studies indicated that Smad4 is the target gene of miR-146a (119,123,124). After miR-146a was transferred, the expression of α-SMA, VIM and Col-1 in injured mice was significantly reduced; however, after simultaneous treatment with Smad4 and miR-146a, the expression of these fibrosis markers was significantly enhanced, suggesting that miR-146 ameliorates skeletal muscle fibrosis by downregulating Smad4 (111). The inflammatory microenvironment, including IL-17, IL-22, IL-6 and other pro-inflammatory cytokines, may induce EMT through TGF-β/Smad or non-Smad signaling pathways (125). miR-146a may be crucial in the process of EMT-related fibrosis mediated by TGF-β.

NF-κB/BMP and endogenous bait receptors for activin membrane-binding inhibitors (Bambi) signaling pathway. In quiescent HSCs, TGF-β1 signaling was suppressed by Bambi, an endogenous decoy receptor for TGF-β (126). In addition to serving as bait, Bambi directly interfered with TGF-β1 signaling by targeting Smad7 (127). Jiang *et al* (128) found that Enhancer of zeste homolog 2 (EZH2) inhibition led to transcriptional block of the TGF-β1 pathway, the cell cycle pathway and numerous ECM components in primary HSCs. EZH2 inhibition reduced the recruitment of H3K27me3 to target genes encoding Bambi and increased Bambi expression. Ni *et al* (19) observed that LPS upregulated H3K27me3 and EZH2 inhibitors increased miR-146a expression by regulating H3K27me3 methylation. This finding suggests that suppressing the recruitment of H3K27me3 around the promoter may increase the expression of miR-146a and Bambi. Under profibrotic stimulation, Bambi expression was downregulated, activating the TGF-β1 pathway of hematopoietic stem cells and activating hematopoietic stem cells (129). LPS is an essential factor in the downregulation of Bambi during cirrhosis progression (130). Bambi is a functional inhibitor of the TGF-β receptor that is downregulated by NF-κB. With the progression of cirrhosis, bacterial translocation and LPS levels increased (131). LPS binds to TLR4 and recruits TRAF6, IRAK1 and TGF-β-activated kinase 1, inducing phosphorylation, ubiquitination and degradation of IκBα. Subsequently, NF-κB dissociates from IκBα and enters the nucleus, inducing downregulation of Bambi, which elevates the response of HSCs to TGF-β1 stimulation (132,133). A gene expression array of total RNA from miR-146a-overexpressed HSC-2 cells and control cells indicated that Bambi mRNA was upregulated in clones overexpressing miR-146a-5p (134). Zou *et al* (107) found that Bambi protein was highly expressed after mi-146a-5p overexpression in TGF-β1-stimulated cells pretreated by LPS.

During fibrosis, miR-146a suppresses the activation of NF-κB by targeting its upstream genes IRAK1 and TRAF6. The expression of Bambi then increases due to the inactivated NF-κB and induces the inhibition of the TGF-β/SAMD signaling pathway. While miR-146a regulates fibrosis, H3K27me3-mediated epigenetic regulation has a considerable role. The effect of miR-146a on fibrosis is summarized in Table I. These findings indicate that miR-146a regulates EMT and fibrotic factors such as α-SMA, COL-1 and COL-4 to exert its antifibrotic functions via these signaling pathways (Fig. 5).

miR-146a regulates fibrosis through fibrosis-related cells Regulation of fibroblasts. Liu *et al* (106) reported that miR-146a downregulated α-SMA expression and myofibroblast transdifferentiation induced by TGF-β1 via inhibiting Smad4. In an isoproterenol-induced cardiac fibrosis model, Zhang *et al* (141) observed that the expression of miR-146a was reduced in cardiac fibroblasts, while α-SMA, Col-1 and fibroblast growth factor 2 were increased. These trends were reversed when miR-146a was upregulated by miR-146a mimics (141). The absence of miR-146a led to the proliferation of synovial fibroblasts due to increased expression of TRAF6 (144). miR-146a mimics decreased the production of α-SMA, Col-1α and fibronectin induced by TGF-β in orbital fibroblasts by targeting Smad4 and TRAF6 (145). These findings suggest that miR-146a participates in fibrocyte differentiation and regulates fibroblast functions via different pathways.

Regulation of macrophages. Macrophages derived from monocytes produce numerous factors, which modulate fibrosis and tissue repair. TGF-β derived from macrophages induces fibroblast migration and promotes fibroblast growth, activation and collagen synthesis (146,147). Due to the essential role of macrophages in regulating fibrosis, researchers adopted several approaches to transfer, reduce and restrain macrophage migration into tissues (148,149). Bhatt *et al* (45) found that the expression of M1 polarization antigens was enhanced, while the expression of M2 polarization antigens was inhibited in miR-146a-deficient macrophages, inducing the infiltration of macrophages and kidney fibrosis. Another study reported that delivery of miR-146a using polyethyleneimine nanoparticles inhibited macrophage infiltration and renal fibrosis *in vivo* (105). Another study found that miR-146a attenuated fibrosis in hepatic schistosomiasis by regulating macrophage differentiation into M2 cells (51). The differentiation of M1 macrophages to M2 macrophages reduced the stimulation of inflammation to fibrosis and promoted matrix remodeling and injury healing (3). There is substantial opportunity for studies on miR-146a regulating macrophages in fibrosis.

5. Application strategies

miRNAs are crucial regulators of gene expression, suggesting that they have the potential to serve as biomarkers for diagnosis and prediction of prognosis, as well as treatment targets for diseases (150).

Table I. Expression patterns and functions of microRNA-146a in different fibrosis models.

Research subject	Target or mediation	Source	Expression	Effect	(Refs.)
Liver fibrosis rats	TRAF6; IRAK1; Smad4; Bambi	HSCs	Down	Abrogation of hepatic fibrosis by suppressing both TGFβ/Smad and NF-κB/Bambi signaling pathways in HSCs	(107)
Radiation-induced liver fibrosis	SRC	HSC LX2	Down	Suppression of α-SMA and Col-1 expression	(110)
Hepatic fibrosis in rats	Smad4	Liver fibrotic tissues	Down	Inhibition of TGF-β1-induced α-SMA expression	(119)
Mice after acute muscle contusion	Smad4	Muscle cells	Down	Attenuation of the effect of TGF-β on the expression of fibrosis markers	(111)
LPS-induced HSC LX2	TRAF6	HSC LX2	Down	Mediates downregulation of TRAF6; suppresses the phosphorylation of Smad2 and attenuates the expression of α-SMA	(135)
Myocardial IRI mice	NOX4	Heart tissues and cardiomyocytes	Down	Regulates the transcription of NOX4, which affects P38 signaling in cardiac fibrosis	(136)
A549 cells treated with TGF-β1	L1CAM	A549 cells	-	Inhibits EMT process via targeting L1CAM	(137)
STZ-induced diabetes in mice	TRAF6; IRAK1	Heart endothelial cells	Down	Reduces the expression of Col-1 α1 and Col-4 α1	(138)
Irradiated HSC LX2	RAC1	HSC LX2	Up	Decreases the expression of α-SMA and Col-1	(139)
Nonalcoholic fibrosing steatohepatitis in mice	Wnt1; Wnt5	Activated HSCs	Down	Decreases the expression of α-SMA and Col-1	(140)
TGF-β1-induced dermal fibroblast	Smad4	Myofibroblast	Up	Reduces the expression of α-SMA	(106)
Isoproterenol-induced cardiac fibrosis in rats	EGF2	Cardiac fibroblasts	Down	Upregulates the expression of basic FGF2, Col-1 and α-SMA	(141)
Constrictive pericarditis-induced MF in rats	TRAF6; IRAK1	Myocardial tissue	8 weeks: Up; 16 weeks: Down	Suppresses myocardial fibrosis by inhibiting TRAF6 and IRAK1 via the TLR-4 signaling pathway	(142)
Human LFH	Smad4	Human LF tissues	Down	Attenuates the progression of TGF-β1-induced fibrosis	(143)

FGF2, fibroblast growth factor 2; Col-1, collagen I; α-SMA, smooth muscle α-actin; MF, myocardial fibrosis; HSCs, hepatic stellate cells; LPS, lipopolysaccharide; IRI, ischemia/reperfusion injury; NOX4, NADPH oxidase 4; L1CAM, L1 cell adhesion molecule; LFH, ligamentum flavum hypertrophy; STZ, streptozotocin; Col-4, collagen 4; SRC, proto-oncogene tyrosine-protein kinase; RAC1, Ras-related C3 botulinum toxin substrate 1; EMT, endothelial to mesenchymal transition; IRAK1, interleukin-1 receptor-associated kinase 1; TRAF6, tumor necrosis factor receptor-associated factor 6; Bambi, BMP and endogenous bait receptors for activin membrane-binding inhibitors.

miR-146a as a biomarker in inflammation and fibrosis

Diagnosis. Due to its significant relationship with inflammation and fibrosis, numerous scientists suggest that miR-146a may be essential for diagnosing related diseases. Shumnalieva *et al* (151) found that miR-146a was overexpressed in peripheral blood compared with a healthy control group. miR-146a was also downregulated in cases with lupus nephritis compared to negative controls, and based on its expression levels, it was possible to identify lupus nephritis and assess its activity (152). Abou-Zeid *et al* (153) found that miR-146a levels were elevated in cases with rheumatoid arthritis and may act as a potentially effective marker of disease activity. Li *et al* (154) reported that miR-146a regulated the inflammatory response during

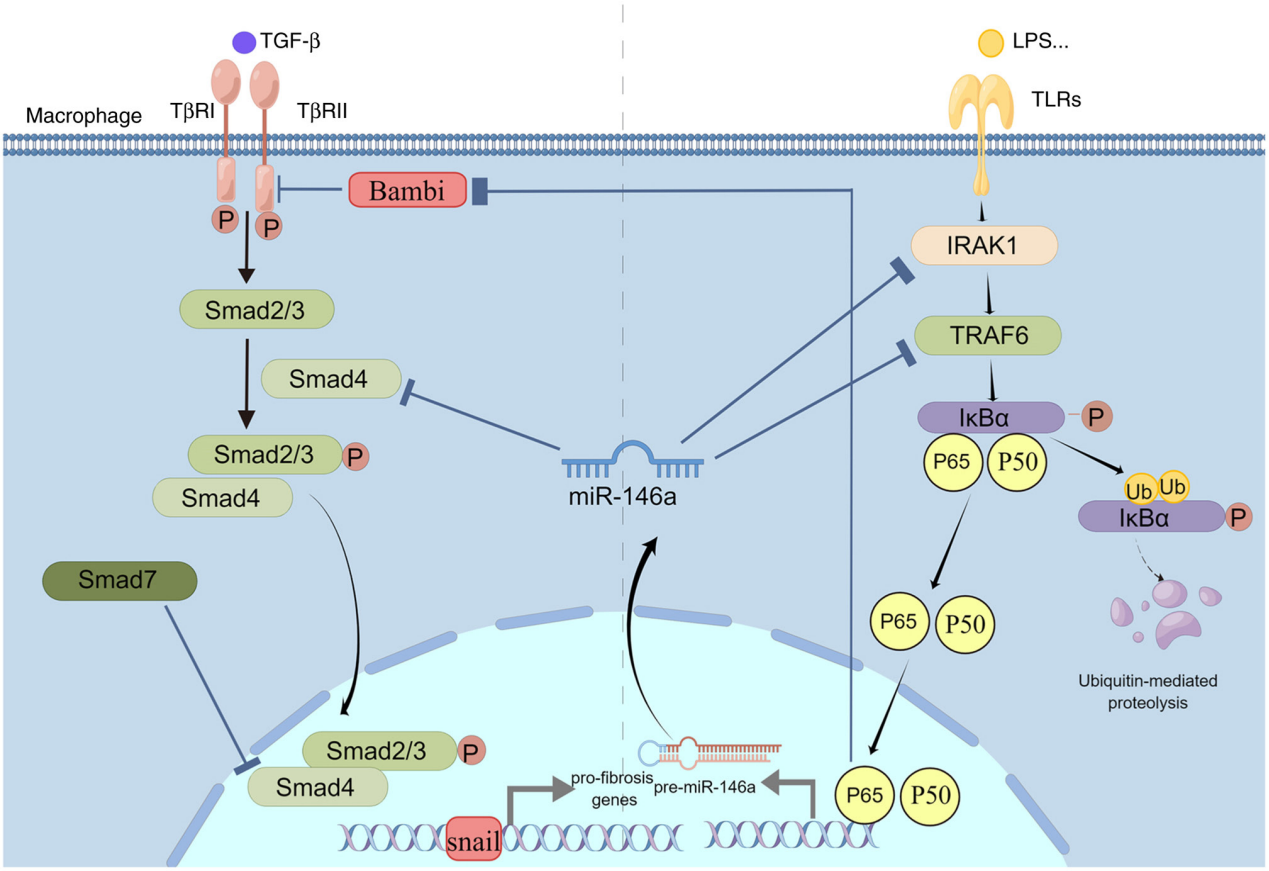

Figure 5. Schematic of miR-146a participating in regulating fibrosis through Smad-dependent TGF-β signaling pathways and the NF-κB/Bambi signaling pathway. MiR-146a inhibits Smad4 combined with the phosphorylation of regulatory Smad2/3 by targeting the 3'UTR of Smad4. By contrast, miR-146a reduces the activation of NF-κB by targeting its upstream IRAK1 and TRAF6 signaling. As a result, the effect of Bambi competing with TβRI for ligand binding increases and suppresses TGF-β/R-Smad signaling. The figure was drawn with Figdraw (https://www.figdraw.com). IRAK1, interleukin-1 receptor-associated kinase 1; TRAF6, tumor necrosis factor receptor-associated factor 6; miR, microRNA; LPS, lipopolysaccharide; TLR, Toll-like receptor; Ub, ubiquitin; Bambi, Bambi, BMP and endogenous bait receptors for activin membrane-binding inhibitors; R-Smad, receptor-mediated Smad; TβRI, type I TGF-β superfamily receptors.

Helicobacter pylori infection via regulating the NF-κB pathway. miR-146a and IL-17A expression were positively correlated in *H. pylori*-infected human gastric mucosa (154). As inflammation has a crucial role in the pathogenesis of acute coronary syndrome, serum exome miR-146a levels were significantly higher in patients than in normal coronary arteries (155). Yang *et al* (156) reported that miR-146a inhibited the accumulation of low-density lipoprotein cholesterol and inflammatory responses by targeting TLR-4 signaling. They also demonstrated that expression levels of miR-146a increased initially and then decreased in atherosclerotic endothelial cells (156). In most fibrosis models, miR-146a expression was downregulated, while certain studies indicated that expression may be upregulated in the early stages of fibrosis (142). These findings suggest that increased miR-146a expression may be a protective factor in early disease stages.

Prognosis. Wu *et al* (157) found that the plasma miR-146a expression and inflammatory factors were positively associated with the severities of osteoarthritis, suggesting that miR-146a levels were able to act as a biomarker of osteoarthritis. Another study on generalized aggressive periodontitis demonstrated higher miR-146a expression in patients than in healthy controls that were directly consistent with disease severity and a reduction in the levels of pro-inflammatory cytokines, suggesting that miR-146a might indicate periodontal disease severity (158). miR-146a reduction was reported by Zhu *et al* (152) to increase the possibility of progression to end-stage renal disease and recurrence within one year. A study on tocilizumab treating multifocal interstitial pneumonia induced by COVID-19 found that in patients with the lowest peripheral expression of miR-146a-5p, the condition was the worst, linking inflammation and COVID-19 evolution (159). Serum exosomal miR-146a-5p levels had the potential to identify mild fibrosis from severe fibrosis and fibrosis (grades I-III) from no fibrosis (160). miR-146a-5p distinguished patients with mild vs. severe fibrosis (161). These findings suggest that miR-146a may serve as a prognostic marker due to its tight relationship with inflammation and fibrosis severity.

Therapy

Direct delivery. The primary challenge for delivering miRNAs is their limited ability to penetrate cell membranes due to their negative charge and rapid degradation *in vivo*. Effective internalization of therapeutic agents into target cells without cytotoxic or immunogenic effects is critical for obtaining

Table II. Applications of delivering microRNA-146a in fibrosis and inflammation models.

Disease	Delivery vectors	Target	Effect	(Refs.)
Microglial-mediated neuroinflammation	hUMSC-Exos	IRAK1; TRAF6	Ameliorates neuroinflammation	(35)
IRI	hUSC-Exo	IRAK1	Inhibits the activation of NF-κB and decreases the infiltration of inflammatory cells	(37)
Renal fibrosis	Polyethylenimine nanoparticles	TRAF6; Smad4	Attenuates renal fibrosis	(105)
NEC	Adenovirus	NLRP3 inflammasome; CLIC4	Attenuates inflammation and intestinal injury in the NEC-affected intestine	(162)
Acute lung injury	Cerium oxide nanoparticles	Col-1α2	Reduces inflammation and decreases collagen deposition	(164)
Allergic rhinitis	Chitosan hydrogel doped with PEG-PLA nanoparticles	NF-κB	Induces less inflammation	(166)
LFH	hUCMSC-EVs	Smad4	Attenuates the progression of TGF-β1-induced fibrosis	(143)
Liver fibrosis	HLSCs-EVs	-	Decreases the expression of α-SMA and Col-1α1	(167)
Myocardial infarction	Exosomes within alginate derivative hydrogel	TRAF6 IRAK1	Induces lower degrees of fibrosis	(169)
Contact dermatitis	NickFect type of cell-penetrating peptides	IRAK1	Reduces ear swelling response and downregulates pro-inflammatory cytokines (IL-6, IL-1β, IL-33 and TNF-α)	(170)
SCCII	Cell permeable peptide	IRAKI; TRAF6	Regulates the neuroinflammatory response	(171)
Injury during mechanical ventilation	Polyethylenimine-lipid nanoparticle	-	Attenuates inflammatory response during mechanical ventilation	(172)

LFH, ligamentum flavum hypertrophy; hUCMSC-EVs, human umbilical cord mesenchymal stromal cell-derived extracellular vesicles; HLSCs-EVs, human liver stem cell-derived extracellular vesicles; PEG-PLA, polyethylene glycol-poly(lactic acid); SCCII, severe controlled cortical impact injury; NLRP3, NACHT, LRR and PYD domains-containing protein 3; NEC, necrotizing enterocolitis; hUMSC-Exos, human umbilical cord mesenchymal stem cell-derived exosomes; IRI, ischemia/reperfusion injury; hUSC-Exo, human urine-derived stem cell-derived exosomes; IRAK1, interleukin-1 receptor-associated kinase 1; TRAF6, tumor necrosis factor receptor-associated factor 6; SMA, smooth muscle actin; Col-1, collagen I.

the desired therapeutic effect, particularly when the aim is to target unwanted inflammation. To date, several substances have been used to develop delivery systems for miR-146a and its mimics, including viral vectors such as adenovirus (162) and nano-carriers consisting of polyethylene glycol-poly (lactic acid) nanoparticles (163), cerium oxide nanoparticles (164) and polyethyleneimine nanoparticles (105). To promote absorption, the nanoparticles are frequently modified with lectins or penetrating peptides (165) or doped with chitosan (166). Although viral vectors possess good stability and transfection efficiency, they may induce adverse inflammatory responses. Therefore, nano-carriers appear to be the primary focus. Studies indicated anti-fibrotic effects after delivering extracellular vesicles containing miR-146a (37,143,167,168). Studies on the delivery of miR-146a to treat inflammation and fibrosis are summarized in Table II. Their treatment effects appear to be dose-dependent.

miR-146a functions as a target. Drugs such as vildagliptin (173) and GSKJ4 (174) attenuated inflammation by regulating miR-146a expression. Other studies reported that inhibition of lncRNAs such as XIST (175) and SNHG16 (176) suppressed inflammatory responses by sponging miR-146a. Knockdown of the lncRNA MALAT1 affected inflammation by increasing miR-146a expression in an LPS-induced acute lung injury model (177). The recombinant *Schistosoma japonicum* protein P40 increased the levels of miR-146a in LX-2 cells and attenuated hepatic fibrosis

by targeting Smad4 (178). Most drugs are designed according to miR-146a function by targeting the promoter of miR-146a, while lncRNAs act via their sponging effect.

6. Conclusions and perspectives

The present study focused on the functions of miR-146a in inflammation and fibrosis. The former may involve the IL-1R/TLRs-NF-κB axis and the JAK-STAT signaling pathway. By regulating microglial M1 and M2 polarization, miR-146a demonstrated critical roles in inflammation and fibrosis. The effects of miR-146a on fibrosis development were discussed in the present study. However, substantial knowledge gaps remain. There was frequent disagreement among the results obtained by different studies, possibly due to preanalytical factors such as acquiring samples, storage and small sample sizes (179). For instance, studies reported that they controlled inflammatory responses via the inhibition of miR-146a expression (173,180), while for inflammation therapy, miR-146a mimics were delivered *in vivo* to upregulate miR-146a levels (176). These principles appear mutually contradictory. In addition, M1 macrophages have a pro-inflammatory effect, while M2 tends to confine inflammation and remodel the matrix or promote fibrosis when inflammation cannot be resolved. Therefore, miR-146a inhibiting M1 polarization of macrophages and promoting M2 polarization may lead to increased fibrosis, while simultaneously serving anti-inflammatory functions, which appears contradictory. A reasonable explanation is that miR-146a promotes a proportional balance between them (51). It should be noted that off-target effects complicate the therapeutic journey, as a single miRNA possesses various targets controlled by cellular substances and environments.

Furthermore, exogenous miRNAs may alter the balance of miRISC-endogenous miRNAs by interacting with miRISC unnecessarily. Treatments based on oligonucleotides, such as miRNA mimics and miRNA inhibitors, should be specific to certain cell types. Synthetic double-stranded miRNAs, which regulate the expression of endogenous miRNA, must be constituted in a manner that allows them to be freely adsorbed by cells, as well as keeping their effectiveness for the intended time (181). A system that is able to deliver the exogenous miRNAs in a standardized and efficient manner should be established. Furthermore, it is necessary to determine mRNA target-specific activity based on a profound comprehension of cellular complexity.

A substantial body of evidence demonstrated that various miRNAs, particularly miR-146a, are essential regulators of inflammation and fibrosis, focusing on the potential of miR-146a as a biomarker and target with a clinical application value. A deeper understanding of the miR-146a-related signaling pathway and its functions will facilitate the early diagnosis and treatment of disease.

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Authors' contributions

ZFL and GFS made all contributions to the design and conception for the study; RJZ performed the literature search; ZFL and GFS wrote and revised the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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