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REVIEW ARTICLE

The Role of miR-146a in Respiratory Diseases with a Focus on COVID-19

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Abstract

Epigenetics is a rapidly expanding scientific discipline, and research into epigenetic regulation in diseases, including infectious diseases, is increasing. As one sort of epigenetic activity, micro-ribonucleic acids (miRNAs) bind to their target messenger RNAs (mRNAs) and regulate their stability and/or translation. This study aims to evaluate non-coding RNAs (ncRNAs) with a focus on miR-146a in COVID-19. In this review, we first describe epigenetics and miRNAs, then explain the significance of miRNAs in disease, with an emphasis on lung diseases. Finally, we examine the role of miRNAs in viral infections, including SARS-CoV-2, with a particular focus on miR-146a. For all relevant studies published between 2000 and 2022, a systematic search of PubMed, Web of Science, Embase, and the Cochrane Library was conducted, limited to English-language studies. Studies were included if they were published between 2000 and 2022, written in English, and directly addressed miR-146a expression or function in respiratory or inflammatory diseases. Non-peer-reviewed sources and studies lacking primary data on miR-146a were excluded. The findings revealed that different types of microRNAs can be useful in the therapy of various lung diseases via different target pathways and genes. Among these, miR-146a has emerged as a key regulator of innate immunity and inflammatory responses in respiratory diseases. miR-146a regulates IL-18 production through modulation of the NF-κB signaling pathway by targeting IRAK1 and TRAF6, which may influence inflammatory responses in severe COVID-19. Furthermore, dysregulation of miR-146a has been associated with enhanced inflammatory responses and disease severity in respiratory viral infections. These findings suggest that miR-146a may serve as a promising biomarker for disease prognosis and a potential therapeutic target in COVID-19 and other respiratory diseases. However, further experimental and clinical studies are required to validate its diagnostic and therapeutic value.

Keywords COVID-19, Epigenetics, MicroRNAs, MiR-146a, Respiratory Diseases

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Introduction

Epigenetic markers can reveal underlying biology, enabling early detection and risk stratification. Coronaviruses and other enveloped RNA viruses can modify the host's epigenome through DNA methylation, making it easier to detect severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in patients before symptoms appear.[1] Additionally, these epigenetic variations help identify individuals at risk of developing severe disease.[2] In epigenetics, two key processes play important roles in differentiation, gene regulation, and carcinogenicity: cytosine methylation in DNA and histone modifications.[3–5] MicroRNAs (miRNAs) are another class of molecules that influence epigenetics and gene expression. They are non-coding RNAs, small molecules with a nucleotide length of around 17–25.[6] A miRNA is produced by transcription from DNA templates to produce primary miRNAs, and then undergoes a process to produce precursor miRNAs, and mature miRNAs produce precursor miRNAs and mature miRNAs. MiRNAs bind primarily to the 3′ UTR of target messenger RNAs (mRNA)[7] and are significant regulators of the gene expression process at the post-transcriptional level. MiRNAs play a decisive role in various biological processes, including cell proliferation, differentiation, growth, and apoptosis.[8] It is estimated that about one-third of genes and their pathways are regulated and controlled by miRNAs. Among these, miR-146a has emerged as a critical regulator of innate immunity and inflammation. It functions primarily by targeting interleukin-1 receptor-associated kinase 1 (IRAK1) and TRAF6, two key adaptor proteins in the Toll-like receptor (TLR) and NF-κB signaling pathways, thereby suppressing downstream pro-inflammatory cytokines, including IL-6, IL-8, TNF-α, and IL-1β. These properties make miR-146a particularly relevant in the context of respiratory diseases, where dysregulated inflammatory signaling plays a central role in disease progression.[9]

Role of miRNAs in respiratory diseases

In this review, we focused on the role of miR-146a in the following lung diseases: chronic obstructive pulmonary disease (COPD), asthma, pulmonary fibrosis, pneumonia, lung cancer, lung inflammation, and SARS-CoV-2, because of their impact on worldwide morbidity and mortality, as well as because their pathophysiology frequently involves inflammation and tissue remodeling. According to reports, non-communicable diseases accounted for 71% of global deaths, with chronic respiratory diseases (CRDs) (7%), second to cancer (16%), and third to cardiovascular diseases (31%).[10] Among the CRDs, COPD and asthma constituted the highest disease burdens.[11]

Lung miRNAs can be divided into three groups according to their function: homeostasis, lung development, and physiological function.[12] Among the miRNAs classified within this group are miR-155, miR-26a, let-7, miR-29, miR-15/miR-16, miR-223, and miR-146a/b.[13] MiR-155 is critical for the lung's immune response, as miR-155-deficient mice exhibit reduced immunity and fail to mount a successful immune response to exogenous stimuli.[14] The second group of miRNAs includes miRNAs involved in lung inflammation and regulation. This group includes miR-146a and miR-146b, which play a role in IL-1 activation during the initial stages of inflammation. TNF-α and other pro-inflammatory cytokines are suppressed by the overexpression of these miRNAs.[15] At the time of infection, miRNAs are important for viral transmission and play a role in viral infection. For example, miR200a and miR223 are involved in lethal influenza virus infection.[15] At the start of severe acute respiratory syndrome (SARS) infection, the upregulation of the miR-17 family, miR-574-5p, and miR-214 was seen.[16] All four viral virulence proteins are targeted by these miRNAs, together with miR-223 and miR-98.[17]MiR-146a functions as a key negative regulator of inflammation by modulating the TLR and NF-κB signaling pathways. Mechanistically, miR-146a directly targets IRAK1 and TRAF6, thereby suppressing downstream pro-inflammatory cytokines such as IL-6, IL-8, TNF-α, and IL-1β. In asthma, miR-146a modulates airway inflammation by regulating NF-κB-dependent chemokine production. In COPD, reduced miR-146a expression contributes to COX-2 upregulation and increased prostaglandin E2 (PGE2) production, promoting chronic inflammation. In pneumonia, miR-146a regulates macrophage polarization via the IRAK1/RXR/LXR axis. In idiopathic pulmonary fibrosis (IPF), miR-146a influences fibroblast inflammatory responses through TRAF6 and IRAK1 inhibition. In SARS-CoV-2 infection, dysregulation of miR-146a may contribute to excessive NF-κB activation, increased IL-18 production, and cytokine storm. The third group of miRNAs is directly implicated in vital lung functions linked to the pathophysiology of pulmonary disease.(Table 1)

Role of mir-146a in respiratory diseases

Despite using the same seed sequence, many miRNAs, including miR-146, are encoded at distinct loci or places in the genome. MiR-146a has been implicated in a variety of processes, including differentiation, inflammation, and the activity of adaptive and innate immune cells. [56,57] Mechanistically, miR-146a acts as a negative feedback regulator of TLR- and cytokine-induced NF-κB activation. Upon inflammatory stimulation, NF-κB induces transcription of miR-146a, which in turn suppresses IRAK1 and TRAF6, creating a self-limiting inflammatory loop. This mechanism is relevant across

Table 1 MiRNAs in lung diseases

Diseases	MiRNA	Gene target	Expression in Disease	Function or type of cell	Ref
Asthma	Mir-155	IL-13Ra1	up	Regulates IL13Ra1 protein	[18,19]
	Mir-145	RUNX3, CFTR	up	Regulates T helper 2 allergic inflammatory responses	[20,21]
	Mir-let-7	IL-13	Up	Regulates IL-13	[22]
	Mir-133a	RhoA	Down	Unknown	[23]
	Mir-21	IL12p35	Up	Regulates immune polarization by targeting IL12p35	[24]
	Mir-9	PP2A	Up	Regulates PP2A activity and DEX-induced glucocorticoid receptor nuclear translocation	[25]
IPF	Mir-29a	ECM-related proteins	Down	Anti-fibrotic	[26–28]
	Mir-26a	HMGA2	Down	Promotes proliferation and differentiation of fibroblasts into myofibroblasts	[29,30]
	Mir-200c	TGF-β1	Down	Unknown	[31]
	Mir-708-3p	ADAM17	Down	Regulates ADAM17 (through GATA/ STAT3 signaling pathway)	[32]
	Mir-let-7d	HMGA2	Down	Inhibits TGF-b	[33]
	Mir-199a-5p	TGF-β	Up	Unknown	[34]
COPD	Mir-146a	COX-2	Down	Negatively correlated with TNF-a, IL-6, IL-8, LTB-4, and LTE-4	[35,36]
	Mir-195	PHLPP2	Up	Regulates Akt signaling	[37]
	Mir-24-3p	BIM	Down	Unknown	[38]
	Mir-15b	SMAD7	Up	Unknown	[39]
	Mir-218-5p	Unknown	Down	Negatively correlated with the number of neutrophils, dendritic cells, and T cells	[40]
	Mir-93-5	NFKBIA	Up	Unknown	[41]
CF	Mir-126	ANO1	up	Regulates PP2A activity and DEX-induced glucocorticoid receptor nuclear translocation	[42]
	Mir-9	ANO1	UP	Bronchial tissues	[43]
	Mir-138	TGF-β1	Down	HLT	[44]
	Mir-145	TGF- β	UP	Serum	[45]
Pneumonia	Mir-708-5p	TLR4	Up	Enhancing the vitality of intracellular bacteria. Regulating the secretion of inflammatory factors	[46]
	Let-7b	TLR4	Down	Promoting the release of pro-inflammatory cytokines, inducing an excessive mucosal immune response	[47]
	Mir-181b	LXA4	Up	Dampening neutrophil infiltration, reducing the release of pro-inflammatory mediators, and limiting collateral tissue damage	[48]
	Mir-29b-2-5p	UNC5C	Down	Favor the balanced intracellular replication to avoid premature cell death. Conducting dissemination to neighboring cells	[49]
	Mir-146a	IL-18	Up	Via NF-κB signaling pathway, which acts on and affects inflammatory genes, such as INF-γ then leads to cytokine storm	[50]
Lung cancer	Mir-338	N K X 2-1	Down	Highly inversely correlated to NKX2-1 expression	[51]
	Let-7a-5p	KRT5	Down	Highly inversely correlated with KRT5 expression	[52]
	Mir-200	ZEB1	Down	Lung cancer tissue	[53]
	Mirna-34a	TGFβR2	Down	Tissue	[54]
	Mir- 146a	TNFα	Down	Via TRAF6 inhibition, it prevents activation of the NF-kβ signaling pathway	[55]

ADAM = a disintegrin and metalloprotease enzyme; ANO1 = anoctamin-1 protein; BIM = a protein that in humans is encoded by the BCL2L11 gene; COX = cyclooxygenase; ECM= extracellular matrix protein; GATA = GATA transcription factors; HLT = human lung tissue; HMGA2 = high-mobility group AT-hook 2 protein; IL = interleukin; INF- γ = interferon – gamma; KRT5 = keratin5 protein; LXA = locus for x-ray sensitivity A repressor;
NF-Kb = nuclear factor kappa-light-chain-enhancer of activated B cells; NFKBIA = Nuclear factor-kappa-B-inhibitor alpha; NKX2-1 = The homeodomain protein NK2 homeobox 2; PHLPP2 = PH domain and leucine rich repeat protein phosphatase-like-2; PP2A = Protein phosphatase 2; STAT3 = Signal transducer and activator of transcription3; TGF- β = transforming growth factor beta; TGFBR2 = Transforming growth factor, beta receptor II; TLR4 = Toll-like receptor 4; TNF- γ = tumor necrosis factor alpha; ZEB1 = Zinc finger E-box-binding homeobox1.

multiple respiratory diseases, with disease-specific variations in miR-146a expression levels and downstream effects as detailed in the following sections.[56,57]

MiR-146a is an important regulator of several immunological mechanisms. It is involved in regulating cytokine overproduction, such as TNF-α, and plays a negative feedback role in innate immunity through TLR signaling, which is linked to bacterial infections by establishing endotoxin tolerance. Lu et al. have recently shown that Mir-146a plays a significant role in inhibiting the function of regulatory T cells. Mice lacking miR-146a were unable to tolerate immune responses, which is due to interferon-gamma-dependent immunity in various organs.[58,59]

MiR-146a's pathogenic activities in respiratory diseases such as pulmonary fibrosis, lung cancer, asthma, and COPD have also been investigated. There has been extensive research on miRNAs in respiratory diseases. For example, the Let-7 gene is recognized for its role as a tumor suppressor, whereas miR-17-92 acts as an oncogene in lung cancer.[60]

In Asthma

Asthma of the airways is the most common chronic disease, causing wheezing and coughing due to airway narrowing.[61] A variety of allergic reactions typically trigger asthma symptoms; therefore, the disease itself is seen as extremely heterogeneous. Depending on the cell types that trigger airway inflammation, asthma could be divided into distinct phenotypes.[62,63] Eosinophilic asthma (EoA) refers to patients with elevated sputum eosinophils (> 3%) whose symptoms are controlled by treatments that suppress eosinophils.[64,65] Neutrophilic asthma (NeuA) characterizes patients with elevated sputum neutrophils (≥ 61%5 or ≥ 64%6).[65,66] When sputum eosinophils and neutrophils are both increased, patients can be classified as having mixed granulocytic asthma (MGA). Finally, patients can be diagnosed with paucigranulocytic asthma (PGA) if there is no evidence of elevated sputum eosinophils or neutrophils and if treatments aimed at suppressing eosinophils and neutrophils are ineffective in controlling symptoms.[65,67] Eosinophilic non-allergic asthma is characterized by type 2 innate lymphoid cells (ILC2) and increased expression of epithelial alarmins. Allergic asthma is characterized by elevated T helper 2 (Th2) responses and levels of IgE.[68,69] Non-EoA is distinguished by airway neutrophilia and Th17 cell involvement.[70,71] The most commonly used asthma treatments are long-acting bronchodilators and inhaled corticosteroids.[72] Human RVs account for roughly 65% of asthma exacerbations induced by viral infections.[73]

Previous studies have shown that numerous components, including IRAK1 and caspase recruitment domain 10 (CARD10) from the NF-κB pathway, are directly targeted by miR-146a/b.[74,75] As a result, it has been demonstrated that miR146a/b is overexpressed in a variety of cell types to suppress endogenous levels of CARD10 and IRAK1 and of NF-κB-inducible chemokines IL-8 and chemokine (C-X-C motif) ligand 1 (CXCL1), as in human bronchial epithelial cells (HBECs).[76] An intriguing example is C-C Motif Chemokine Ligand 5 (CCL5), which is inhibited directly by miR146a and indirectly via IRAK1 and CARD10.[77] Numerous asthma studies have identified altered miR-146a expression,[78–82] and Kivihall et al. previously showed that the development of the NeuA phenotype may be related to lower miR-146a expression in human airway epithelial cells.[76] However, in the study by Laanesoo et al., they expected that miR146a/b would be involved in regulating immunological responses to RV infections in bronchial epithelial cells and the airways, as well as in asthma exacerbations. They also demonstrated and investigated the expression and function of miR146a/b during RV infection in HBECs and in mouse models of RV-induced airway inflammation, RV-induced aggravation of allergic airway inflammation, and inflammation induced by house dust mite extract (HDM). They demonstrate that miR146a can suppress inflammatory responses to RVs in HBECs as well as during RV and/or HDM-induced airway inflammation; as a result, mice lacking miR146a/b have less prominent type 2 cell responses in mouse models of HDM-induced allergic airway inflammation and RV-induced exacerbation of allergic airway inflammation.[83]

In COPD

In recent decades, COPD has gained increasing attention due to its high mortality rate and fatal comorbidities.[84] COPD will become the third leading cause of mortality worldwide by 2030, and the incidence is currently growing in emerging nations.[85] Few studies have focused on the role of miRNAs in COPD. Sato et al. found that the pulmonary fibroblasts of COPD patients present less expression of miR-146a after stimulation with pro-inflammatory cytokines when compared with non-COPD patients that had similar smoking histories.[86] This results in the overexpression of cyclooxygenase-2 (a target of miR-146a) and an increase in the production of PGE2. The expression of post-stimulation miR-146a and PGE2 production is both linked to disease severity, as assessed by forced expiratory volume in one second (FEV1).[86] Investigation of miRNA profiles in COPD patients' induced sputum reveals differences from non-smokers or smokers without airflow obstruction.[87] Specifically, the expression of miR-146a and let-7c is lower in patients with COPD who continue to smoke than in smokers without airway obstruction. In this study, the reduction in miR-146a may be a determinant of the inflammatory state and the progression of COPD. Furthermore, while accounting for the decrease in levels

of let-7 is associated with carcinogenesis, alterations in the expression of particular miRNAs may lead to an increased risk of lung cancer in COPD patients.[87,88] Recently, Ezzie et al. reported on miRNA levels in the lung tissue of smokers with and without COPD.[89] The two groups showed seventy miRNAs with varying degrees of expression. Some of these changes, such as the increase in members of the miR-15/107 family, may affect important signaling pathways involved in the development of COPD, including transforming growth factor β (TGF-β) and Wnt proteins. Other key miRNAs for muscle biology, such as miR-206, miR-208, or miR-499, did not show significant differences between COPD patients and healthy individuals.[90]

Pneumonia

Pneumonia, a lower respiratory infection, is usually caused by microorganisms such as viruses, bacteria, and fungi. Shortness of breath, cough, chest pain, fever, respiratory failure, and heart failure are common symptoms.[91,92] Especially among children and seniors, pneumonia has one of the highest mortality and morbidity rates in the world.[93–95] It is commonly recognized that pneumonia is linked to microorganisms, stimulating inflammation by microorganisms, for instance, endotoxins, which are a major cause of severe pneumonia.[96] Among miRNAs, miR-146a-5p reveals an inflammatory inhibition effect in many tissues and cells, including human airway smooth muscle.[96,97] In particular, miR-146a regulates the repolarization of human alveolar macrophages and the secretion of inflammatory cytokines in vitro.[98] Ramkaran et al. identified miR-146a as a potential target to reduce inflammation in individuals with coronary artery disease. These findings suggested that miR-146a has potential as a target for regulating lung inflammation.[99]

Li et al. demonstrated that miR-146a-5p expression was decreased in pneumonia. It has been hypothesized that miR-146a-5p inhibits ABCG1 production and inflammation through the IRAK-1/RXR/LXR signaling pathway. They suggested that miR-146a-5p exerts a unique anti-inflammatory effect in pneumonia, indicating that it may be a potential therapeutic target.[100] Lo et al. reported that miR-146a-5p mediates high glucose-induced endothelial inflammation via targeting IRAK1 expression.[101]

IPF

IPF is a chronic illness characterized by the development of scar tissue in the lungs, leading to decreased gas exchange and limited airflow. The disease's basic causes remain unclear, but it is believed that persistent epithelial injury or exposure to pathogens drives an exaggerated wound-healing response by fibroblasts, contributing to the development and progression of IPF.[102–104] In this respiratory disease, the role of IL-1 remains undetermined, despite reports of elevated levels in bronchoalveolar lavage fluid.[105] Additionally, there are contradictory studies on whether IL-1 induces pro- or anti-fibrotic activity.[106] IL-1 has already been demonstrated to induce IL-6 expression in orbital and synovial fibroblasts in vitro, although its impact on lung fibroblasts is unknown.[107]

There is currently a substantial body of research indicating that miRNAs are key regulators of the immune response.[108] In particular, elevations of miR-146a and miR-155 have been discovered to be inflammatory response regulators in numerous cell types.[109,110] However, long non-coding RNAs (lncRNAs) are poorly understood in terms of function and mechanism of action, which are typically classified as long intergenic ncRNA (lincRNA) (placed between protein-coding genes), antisense (whose transcription overlaps protein-coding genes on the opposite strand), and pseudo-genes (non-translated copies of protein-coding genes).[111,112] However, either through interactions with proteins and/or RNA/DNA pairing, there is currently accumulating evidence that lncRNAs are new regulators of a variety of biological responses, including inflammation.[113,114] Indeed, our and others' research has revealed a number of lncRNAs that are differently expressed when innate immunity is activated and that have been found to regulate the ensuing inflammatory response, including p50-associated COX-2 extragenic RNA (PACER),[115] TNFα- and hnRNPL-related immune-regulatory lincRNA (THRIL),[116] IL1β-RBT46,[117] lnc-IL7R,[118] lincRNA-EPS,[119] lincRNA-Tnfaip3, IL7AS,[120] and lincRNA-COX2.[121,122] The knockdown of MIR3142HG showed that this lncRNA was a positive regulator of the release of IL-8 and CCL2, in contrast with IL7AS. The results of a subsequent analysis of miRNA expression showed that MIR3142HG was metabolized to miR-146a but not miR-3142, which might indicate that the biological actions of MIR3142HG are secondary to the production of miR-146a. Unfortunately, there is no way to separate the actions of MIR3142HG from those of miRNA-146a; the knockdown of miRNAs is also expected to reduce host gene expression. However, miR-146a is a well-studied miRNA that has previously been shown to suppress the inflammatory response by down-regulating TRAF6 and IRAK1. In human lung fibroblasts, this miRNA has a different function and mechanism of action if it is mediated by miR-146a.[123,124]

Wittmann. et al. The subsequent comparison with IPF fibroblasts revealed no changes in IL-1β-induced IL7AS production, but there was an important reduction in the generation of MIR3142HG and miR-146a, which was associated with a decrease in IL-6, IL-8, and CCL2 release. Given that MIR3142HG knockdown drastically inhibits IL-8 and CCL2 release and partially reduces IL-6 release in control fibroblasts, this suggests that the

decrease in MIR3142HG expression may be the cause for the lower inflammatory response in IL-1-stimulated IPF fibroblasts.[125]

In lung cancer

Many researchers have focused on miRNAs and their function in signaling pathways controlling cancer progression.[126] A large variety of miRNAs, including miR-146a, can have a crucial role in cancer cell proliferation, invasion, cell survival, migration, and metastasis. Changes in microRNA expression may play a crucial role in a variety of cancers, including lung cancer, as compared to normal tissues.[127] According to Bertoli et al., numerous miRNA subgroups play a crucial role in many breast cancer markers.[128] It has been suggested that miR-146a may have a role in various hallmarks of lung cancer, such as resisting cell death, evading growth barricades, cell proliferation, tumor immune tolerance, inflammation, energy metabolism imbalance (Warburg effect), promoting angiogenesis, metastasis, and genome fragility, which were initially described by Hanahan and Weinberg.[129] The dysregulation of miRNAs has been seen in nearly every type of tumor, so it is likely that they are involved in the hallmarks of cancer. Apart from lung cancer hallmarks, miR-146a has already been implicated in cancer stem cells (CSCs). Between EMT and CSC formation, there is a similarity, as each has many common signaling mediators like Notch, Wnt, and Hedgehog proteins. Several reports have revealed stem cell-like features, suggesting that they share essential signaling pathways and drug resistance phenotypes with CSCs.[130,131]

The relationship between MiR-146a and lung inflammation and SARS-COV-2

Accumulating evidence indicates that chronic inflammation underlies obesity, diabetes, and atherosclerotic coronary disease. A key participant in chronic inflammation is the feed-forward loop involving the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), which increases pro-inflammatory cytokines, including IL-1, IL-6, TNF-α, and IFN-γ, which, in turn, stimulate NF-κB.[132] MiR-146a is triggered in response to inflammation to reduce inflammation. NF-B promotes the production of miR-146a, which has a negative impact on IL-1 and TNF receptors.[133] Downregulation of circulatory miR-146a or miR-146a deficiency is associated with inflammatory disorders manifested in various organs (lungs, heart, brain, or skin) and underlying vascular or autoimmune diseases. Recognition of viral infection by pattern-recognition receptors, such as TLRs, initiates the innate immune response, which includes changes in miRNA expression and leads to modulation, augmentation, or suppression of cytokine responses. MiR-146a is considered to be the dominant regulator of TLR- downstream signaling.[134] Namely, miR-146a targets and suppresses several downstream TLR- signaling molecules, such as IRAK1, interferon regulatory factor 5 (IRF5), and tumor necrosis factor receptor-associated factor 6 (TRAF6), in order to avoid excessive inflammation after infection.[133] Given its significance in host antiviral defense mechanisms, it is not surprising that viruses could develop mechanisms for interfering with host miRs. In a study by Liu et al. Among 28 human miRNAs predicted to target the SARS-CoV-2 genome, miR-146 was reported as one involved in immunity modulation.[135] The virus could alter miR activity by binding and sequestering free miR or can alter miR expression and miR-mediated protein expression, thus affecting viral replication and host immune responses. For example, IFN-signaling is a critical cascade of events induced by viral infection, leading to upregulation of IFN-stimulated genes that inhibit viral replication. Viruses have developed various mechanisms to evade the IFN system, such as through changes in host miR-146a. Namely, enterovirus- EV71, dengue virus, HBV, or influenza A virus, by induction of miR-146a in infected cells, could negatively regulate the IFN-signaling.[136] Moreover, miR-146a negatively regulates IFN-γ production in natural killer cells (NK cells) by targeting IRAK1 and TRAF6, with subsequent inhibition of the NF-κB signaling cascade. IFN-γ is a critical cytokine produced by activated NK cells, which function in immune defense to eradicate both virus-infected cells and tumor cells. However, it is observed that miR-146a suppresses effects only after NK cells receive excessive co-stimulation of IL-12 and IL-18 or become super active, suggesting that miR-146a induction would be initiated to “fine-tune” the immune response of NK cells into an appropriate range.[137] Likewise, it is also suggested that miR-146a may negatively regulate the cytotoxicity of NK cells.[138] In line with the proposed protective role of miR-146a in SARS-CoV-2, Masselli et al. pointed out that upon SARS-CoV-2 infection, NK cells likely exit the peripheral blood, traffic into the lung, where they potentially enhance local inflammation and injury.[139] Thus, miR-146a may, by “fine-tuning” NK cells, contribute to the balance between NK cells’ beneficial antiviral and detrimental pathologic effects in the lungs of COVID-19 patients. Furthermore, miR-146 deficiency observed in diabetes leads to enhanced inflammation (by insufficient inhibition of IRAK1/TRAF6), fibrosis (by fibronectin expression), and increased synthesis of MCP-1, followed by further reduction of miR-146a (by enhancing TGF-β1/ErbB4/Notch1 signaling),[139] systemic effects accompanying severe COVID-19 [140] (Figure 1)(Table 2).

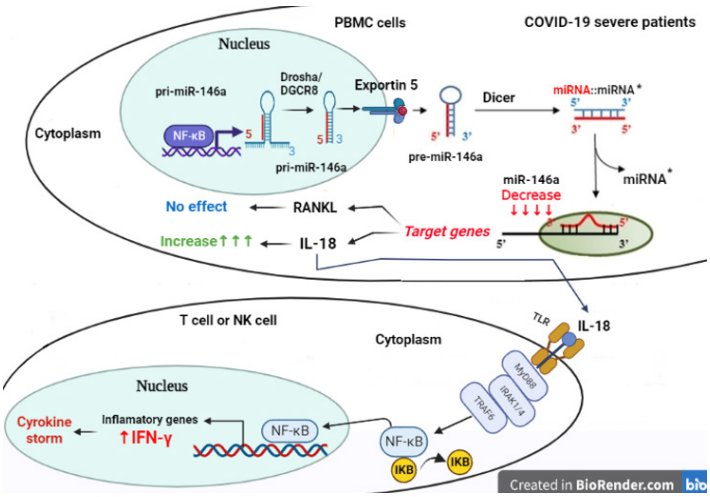

Figure 1 MiR-146a and IL-18 mechanism of function in the pathogenesis of COVID-19. SARS-CoV-2 induces inflammation and severe ARDS through four mechanisms. According to our study, as shown in the Figure, miR-146a decreases with increasing COVID-19 severity; however, the effect on serum IL-18 increased significantly in the severe group but did not affect RANKL. IL-18, via the NF-κB signaling pathway, affects T cells and NK cells, especially inflammatory genes such as INF-γ. Finally, INF-γ is increasing and leads to a cytokine storm.

Table 2 The relationship between miR-146a and target genes

Disease type	Gene target	Source	Effects	Associated phenotype(s)	Ref
MS	↓ FAF1	PB	Up ↑	Inhibition of T cell apoptosis, higher production of IL-17, and differentiation of Th17 lymphocytes	[141]
	N/A	Active brain lesions	Up ↑	N/A	[142]
Psoriasis	↓ IRAK1	PBMCs	Up ↑	Higher production of IL-17 and PASI, higher disease severity	[143,144]
	↑ IRAK1	Skin lesions	Up ↑	Increased expression of IL-17 and PSI, reduced keratinocyte proliferation	[145-147]
GD	ACKR2 ↓	Keratinocytes	Up ↑	Inflammation diffusion	[148]
	N/A	Thyroid tissue	Down ↓	N/A	[149]
	N/A	Plasma	Down ↓	Upregulation of IL-17 serum level, increased disease activity, and CAS	[150]
GO	NUMB ↑	PBMCs	Down ↓	Abnormal cell differentiation, progression of orbital inflammation, and development of orbital lesions development	[151]
	↓ Notch2	Orbital tissues	Up ↑	Increase of disease activity, upregulation of survival, differentiation, proliferation, and apoptosis inhibition in orbital fibroblasts, dysregulation of IL-6 production, inhibition of TGF-β signaling pathway, and prohibition of orbital fibrosis	[152]
SS	↑ TRAF6	PBMCs	Up ↑	Activation of inflammatory pathways such as NF-κB, chronic inflammation, and severity, increases VAS scores for parotid gland swelling and dry eyes, and increases disease activity	[153,154]
	↑ IFNs	B lymphocytes	Down↓	Inflammation stability	[155]
	N/A	Serum	Up ↑	Intensification of inflammatory responses, development of renal injuries, and pulmonary interstitial lesions	[156]
	↓ CD80	Salivary glands	Up ↑	Prohibition of the Tregs function, increase of the effector T lymphocytes activity, deviation of the immune responses towards the activation of auto-reactive cells, chronic inflammation, and disease progression	[156,157]
T1D	↓ TRAF6 IRAK1 (SC)	Sciatic nerve	Up ↑	Increased activity of the NF-κB pathway in the sciatic nerve, high levels of production of TNF-α, IL-6, and IL-1β, and diabetic neuropathy development	[158]

	N/A	Retina	Down ↓	Elevated expression of inflammatory factors and ECM proteins, including TNF-α, IL-6, IL-1β, fibronectin, and Col4α1, as well as the p65 subunit of the NF-κB in retina, disruption to the function of retina, and diabetic retinopathy incidence	[159-161]
	N/A	Renal tissues	Down ↓	Elevated expression of inflammatory factors and ECM proteins, including TNF-α, IL-6, IL-1β, fibronectin, and Col4α1, as well as the p65 subunit of the NF-κB in kidneys, disruption to the function of kidneys, and diabetic nephropathy incidence	[159,162]
Asthma	N/A	Serum/Plasma	Up ↑	Increased number of blood eosinophils, higher disease activity	[163-166]
	N/A	Splenic CD4+ T lymphocytes	Up ↑	Increased number of inflammatory cells in their BALF	[166]
	N/A	Bronchial tissue	Down ↓	Increased production of CCL20 chemokine by ASMCs, CMH in patients, and death	[167]
	N/A	Lung tissue	Up ↑	Re-regulation of proliferation and apoptosis of BSMCs decreased disease severity.	[168]
RA	IRAK1 (SC) TRAF6 (SC) FAF1 ↓	PBMCs	Up ↑	Increased tender and swollen joint count and DAS28, elevated ESR and CRP levels, increased Th17 cells differentiation and IL-17 production, T lymphocytes resistance against apoptosis, chronic inflammation, and higher disease activity	[169-173]
	↓ FAF1	Synovial tissues	Up ↑	Increased Th17 cells differentiation and IL-17 production, T lymphocytes resistance against apoptosis, chronic inflammation, and higher disease activity	[172,174, 175]
	↑ STAT1	Tregs	Down↓	Tregs' inflammatory phenotype and production of TNF-α, IFN-γ, and IL-17 by these cells increased disease activity	[176]
Cancer, inflammation, and innate immune response	IRAK1/ TRAF6 ↓	Leukemic monocyte cell line	Up ↑	Inhibition of NF-κB signaling	[177]
	TRAF6 ↑	Hematopoietic stem and progenitor cells	Down↓	5q- syndrome	[178]
	IRAK1/ TRAF6 ↓	breast cancer cell	Up ↑	FOXP3-induced cellular apoptosis	[179]
Cardiovascular disease	IRAK1/ TRAF6 ↓ (in vitro)	peripheral blood mononuclear cells	Up ↑	Coronary artery disease	[180]
	IGSF1, SORT1, and NOVA1 ↓	Patient arteries	Up ↑	Atherosclerotic plaque formation	[181]
	IRAK1/ TRAF6 ↓	Cardiac tissue: cardiac myocytes and monocytic cells	Up ↑	Cardio protection in microbial sepsis	[182]
	RNase L ↓	myocardial tissue	Up ↑	cyanotic congenital heart disease and chronic hypoxia	[183]

Abbreviations: ACKR2 = atypical chemokine receptor 2; anti-dsDNA= anti-double strand DNA; AS= ankylosing spondylitis; ASMCs= airways smooth muscle cells; BAL= bronchoalveolar lavage; BALF= bronchoalveolar lavage fluid; BASDAI= bath ankylosing spondylitis disease activity index; BD= behcet's disease; BSMCs= bronchial smooth muscle cells; CAS= clinical activity score; CCL19= C-C motif chemokine ligand 19; CCL20= C-C motif chemokine ligand 20; CD4= cluster of differentiation 4; CD40= cluster of differentiation 40; CD80= cluster of differentiation 80; CD86= cluster of differentiation 86; CMH= chronic mucus hypersecretion; Col1α1= collage, type 1, alpha; Col4α1, collage, type 4, alpha 1; CRP= C-reactive protein; DAI= disease activity index; DAS28= 28-joints disease activity score; DKK1= dickkopf-1; DM= dermatomyositis; ECM= extracellular matrix; eGFR= estimated glomerular filtration rate; EGFR= epidermal growth factor receptor; ESR= erythrocyte sedimentation rate; FAF1= Fas-associated factor-1; GADA= glutamic acid decarboxylase antibody; GD= Graves disease; GO= Graves' ophthalmopathy (orbidopathy); IBD= inflammatory bowel disease; ICAM-I= intercellular adhesion molecule 1; IFN= interferon; IFN-γ= interferon-gamma; IL-1β= interleukin 1 beta; IL-6= interleukin 6; IL-8= interleukin 8; IL-17= interleukin 17; IRAK1= interleukin-1 receptor-associated kinase 1; ITP= immune thrombocytopenia; LECs= limbal epithelial cells; MCP-1= monocyte chemoattractant protein-1; MG= myasthenia gravis; MS= multiple sclerosis; MyD88= myeloid differentiation primary response 88; NF-κB= nuclear factor kappa light chain enhancer of activated B cells; OLP= oral lichen planus; PBMCs= peripheral blood mononuclear cells; PB= peripheral blood; PSI= psoriasis severity index; PASI= psoriasis area and severity index; RA= rheumatoid arthritis; REG3A= regenerating islet-derived protein 3-alpha; SC= similar to controls; SLE= systemic lupus erythematosus; SLEDI= systemic lupus erythematosus disease activity index; SS= sjogren ¨ 's syndrome; SSc= systemic sclerosis; STAT1= signal transducer and activator of transcription 1; T1D= type 1 diabetes mellitus; TGF-β= transforming growth factor beta; Th1 cells= T helper type 1 cells; Th2 cells= T helper type 2 cells; Th17 cells= T helper type 17 cells; TLR4= toll-like receptor 4; TNF-α= tumor necrosis factor alpha; TRAF6= tumor necrosis factor receptor-associated factor 6; Tregs= regulatory T cells; VAS= visual analog scale; VCAM= vascular cell adhesion molecule.

Future Directions and Perspective

From a therapeutic standpoint, the immunomodulatory role of miR-146a makes it an attractive candidate for RNA-based interventions. miR-146a mimics, synthetic molecules that restore miR-146a function, have shown promise in preclinical models of inflammation and viral infection by dampening NF-κB activity and reducing cytokine storm. Conversely, miR-146a inhibitors (antagomirs) may be relevant in contexts where excessive miR-146a suppression of antiviral immunity is undesirable. However, several challenges must be addressed before clinical application, including efficient delivery to lung tissue, off-target effects, and ensuring molecular stability in vivo. While no completed clinical trials specifically targeting miR-146a in COVID-19 have been published to date, its central role in inflammatory regulation positions it as a strong candidate for future RNA therapeutic development

MiR-146a is a key regulator in both inflammation and innate immunity. Recent findings suggest that when it is not regulated properly, it contributes to the onset, progression, and severity of respiratory viral infections, especially COVID-19. This makes miR-146a a promising epigenetic marker for early disease detection, risk assessment, and treatment response monitoring. Future research should focus on: (1) longitudinal studies tracking miR-146a expression across early, acute, and recovery stages of COVID-19 in diverse patient populations including the elderly and immunocompromised; (2) preclinical studies evaluating miR-146a mimic delivery via lipid nanoparticles or exosome-based systems in ARDS and cytokine storm models; and (3) validation of miR-146a combined with IL-18 as a dual biomarker panel for early severity stratification in respiratory viral infections. Additionally, investigation into the interaction between miR-146a and other non-coding RNAs, such as lncRNAs (e.g., MIR3142HG), warrants further exploration given its relevance in IPF fibroblast responses described in this review.

Additionally, modifying miR-146a with miRNA mimics or inhibitors presents a new way to restore immune balance and reduce severe inflammatory reactions like cytokine storms. However, there are challenges to consider, including delivery systems, unintended effects, and molecular stability, that need to be carefully managed before applying these strategies in clinical settings. Overall, miR-146a serves as a crucial link between host immunity and viral infection, offering a promising area for developing targeted epigenetic and RNA-based treatments for respiratory diseases.

Conclusion

Based on previous studies, there is no specific therapy for COVID-19, and the most important dysregulated miRNAs identified in the selected articles may play a key role in COVID-19. Due to the importance of miRNAs in pulmonary diseases, especially infectious viral diseases such as SARS-CoV-2, they may be potential candidates for targeted therapy to reduce morbidity and mortality, as miR-146a and its correlation with IL-18 can be used as early prognostic and diagnostic markers. However, further research is needed to elucidate the exact effect of miR-146a on the pathogenesis of COVID-19 for clinical use.

Declarations

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During the preparation of this manuscript, the authors used AI-based language tools to improve the clarity and readability of the text. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication

Authors' Contributions

Shahriar Alipour contributed to the study conception, design, literature search, and manuscript drafting and revision. Karmand Hamad Khdhir contributed to the literature search and data extraction. Nazanin Chehreghani contributed to manuscript drafting and critical revision. All authors read and approved the final manuscript.

Availability of Data and Materials

Not applicable, as this is a review article and no new datasets were generated or analyzed.

Conflict of Interest

The authors declare that there are no conflicts of interest.

Consent for Publication

Not applicable.

Ethical Considerations

As this article was written as a review, no Code of Ethics was obtained for this project, and it did not require informed consent or have a funding source.

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