International Journal of General Medicine

Dovepress
open access to scientific and medical research

Open Access Full Text Article

REVIEW

Advances in the Study of Non-Coding RNA in the Signaling Pathway of Pulmonary Fibrosis

Dengyun Pan, Xin Di, Bingdi Yan, Xiaomin Su

Department of Respiratory Medicine, The Second Hospital of Jilin University, Changchun, People's Republic of China

Correspondence: Bingdi Yan; Xiaomin Su, Department of Respiratory Medicine, The Second Hospital of Jilin University, 218 Ziqiang Street, Changchun, 130041, People's Republic of China, Email yanbingdi@jlu.edu.cn; suxiaomin@jlu.edu.cn

Abstract: Pulmonary fibrosis is a group of chronic, progressive, and irreversible interstitial lung diseases, which are common to most end-stage lung diseases and are one of the most difficult diseases of the respiratory system. In recent years, due to the frequent occurrence of air pollution and smog, the incidence of pulmonary fibrosis in China has increased year by year, the morbidity and mortality rates of pulmonary fibrosis have gradually increased and the age of the disease tends to be younger. However, the pathogenesis of pulmonary fibrosis is not yet fully understood and is needed to further explore new drug targets. Studies have shown that non-coding RNAs play an important role in regulating the process of pulmonary fibrosis, non-coding RNAs and their specifically expressed can promote or inhibit the process. Here, we review the role of some in the regulation of pulmonary fibrosis signaling pathways and provide new ideas for the clinical diagnosis and treatment of pulmonary fibrosis.

Keywords: pulmonary fibrosis, MicroRNA, LncRNA, CircRNA, signaling pathways

Introduction

Pulmonary fibrosis is a terminal change of interstitial lung disease (ILD). It is an abnormal repair process in cases of persistent microdamage to the alveolar epithelium caused by a variety of factors, during which, as the inflammatory response progresses, fibroblasts proliferate and differentiate abnormally, and the extracellular matrix accumulates excessively leading to scar formation in the lung.[1,2] As the disease worsened, altered normal lung tissue structure, reduced compliance, and restricted gas exchange, leading to progressive loss of lung function and eventually respiratory failure and even death. In recent years, the exploration of the pathogenesis and treatment of pulmonary fibrosis at the genomic level has become a major research hotspot,[3] especially in the area of non-coding RNAs (ncRNAs).[4]

Non-coding RNAs are RNAs that do not encode proteins. The common feature of these RNAs is that they can be transcribed from the genome, but are not translated into proteins and can perform their respective biological functions at the RNA level.[5] This review focuses on outlining the targets of some miRNAs, lncRNAs, and circRNAs among ncRNAs in the signaling pathway of pulmonary fibrosis, and we look forward to providing a theoretical basis for the clinical management of pulmonary fibrosis.

Targets of MiRNA in the Pulmonary Fibrosis Signaling Pathway

MiRNAs are a class of small ncRNAs about 20–24 nucleotides long encoded by endogenous genes. It is involved in a variety of important physiological and pathological processes in the body, mainly by degrading target mRNAs or inhibiting their translation level through base pairing with the untranslated region at the 3' end of the target mRNA.[6,7] MiRNAs are up- or down-regulated in fibrotic lung tissues. Therefore, they are divided into pro-fibrotic miRNAs and anti-fibrotic miRNAs (Table 1). Hence, targeting these differentially expressed miRNAs could provide a potential therapeutic strategy for pulmonary fibrosis.

Received: 8 January 2024
Accepted: 24 March 2024
Published: 10 April 2024

Table 1 Expression Levels and Targets of miRNAs in Pulmonary Fibrosis

MiRNAs	Signaling Pathways	Expression	Effect	Target
miR-21	TGF-β/Smad	Increase	Pro-fibrotic	Smad7
miR-26a	TGF-β/Smad	Decrease	Anti-fibrotic	Smad4
miR-29b	TGF-β/Smad	Decrease	Anti-fibrotic	TGF-β1 mRNA 3'-UTR
miR-140	TGF-β/Smad	Decrease	Anti-fibrotic	Smad3
	Wnt			OGN
miR-486-5p	TGF-β/Smad	Decrease	Anti-fibrotic	Smad2
miR-326	TGF-β/Smad	Decrease	Anti-fibrotic	TGF-β1-3'UTR
miR-34a-5p	TGF-β/Smad	Decrease	Anti-fibrotic	Smad4
miR-221	TGF-β/Smad	Decrease	Anti-fibrotic	HMGA2
miR-448-5p	TGF-β/Smad	Decrease	Anti-fibrotic	Six1
miR-34c-5p	PI3K/Akt	Decrease	Anti-fibrotic	Fra-1
miR-503	PI3K/Akt	Decrease	Anti-fibrotic	PI3K p85
miR-524-5p	PI3K/Akt	Decrease	Anti-fibrotic	Itga6
miR-506	NF-κB	Decrease	Anti-fibrotic	NF-κB p65
miR-627	NF-κB	Decrease	Anti-fibrotic	HMGB1
miR-27a-3p	Wnt	Increase	Anti-fibrotic	Wnt3a
miR-338	Hedgehog	Decrease	Anti-fibrotic	SMO
miR-30d	Notch	Decrease	Anti-fibrotic	JAG1

The TGF-β/Smad Pathway in Pulmonary Fibrosis

Transforming growth factor-β (TGF-β) belongs to the TGF-β superfamily, a group of regulatory cytokines. It plays an essential role in cell growth, differentiation, extracellular matrix synthesis, apoptosis, immunosuppression, and damage repair. Of the three isoforms of TGF-β, TGF-β1 is considered a key factor in the development of pulmonary fibrosis.[8,9] In pulmonary fibrosis, TGF-β1 acts in five ways:[9–14] (1) by promoting extracellular matrix deposition; (2) by promoting the proliferation and aggregation of fibroblasts and their conversion into myofibroblasts; (3) by promoting the epithelial-mesenchymal transition (EMT) process; (4) by regulating immune responses and performing microenvironmental modifications; (5) by acting as a pro-angiogenic factor, to promoting angiogenesis in fibrotic areas; and (6) by inducing multiple cells to secrete senescence-associated secretory phenotypes that drive pulmonary fibrosis through senescence.

Smad proteins are a class of intracellular signaling molecules downstream of the TGF-β superfamily, and they play an important role in transmitting TGF-β signals from the extracellular to the nucleus. In the TGF-β/Smad signaling pathway, TGF-β ligands bind to heterodimeric complexes of type II and type I receptors, phosphorylating type II receptors and activating type I receptors. Activated type I receptors phosphorylate Smad2 and Smad3. Smad2/3 dimer forms a trimeric complex with Smad4 and translocates to the nucleus to positively or negatively regulate the transcription of target genes.[15,16] Smad7 in the Smad family not only inhibits the transcriptional activity of the Smad complex, but also competes with R-Smad to interact with type I receptors, leading to negative regulation of TGF-β/Smad signaling pathway[17] (Figure 1).

MiR-21 is widely present in human cells and tissues, and its dysregulation is closely associated with the development and progression of pulmonary fibrosis. Liu et al[8] found that miR-21 expression was upregulated in myofibroblasts in a bleomycin (BLM)-induced pulmonary fibrosis model of mice. Meanwhile, they also found that introducing miR-21 antisense probes for experimental mice or knocking out the miR-21 gene, on the other hand, attenuated the degree of lung fibrosis. This suggests that miR-21 can promote the development and progression of pulmonary fibrosis. TGF-β1 upregulates miR-21 expression through the Smad pathway, while increasing miR-21 levels and inhibiting Smad7 expression, thereby enhancing the pro-fibrotic level of TGF-β1 in fibroblasts. Thus, miR-21 not only plays a synergistic role with TGF-β1 in the process of pulmonary fibrosis, but also acts as an amplifier of TGF-β1 signaling in the signaling pathway.

MiR-26a expression was downregulated in both experimental lung fibrosis mice and idiopathic pulmonary fibrosis (IPF) patients. Overexpression of miR-26a inhibited TGF-β1-induced fibrosis in MRC-5 human fetal lung fibroblasts and

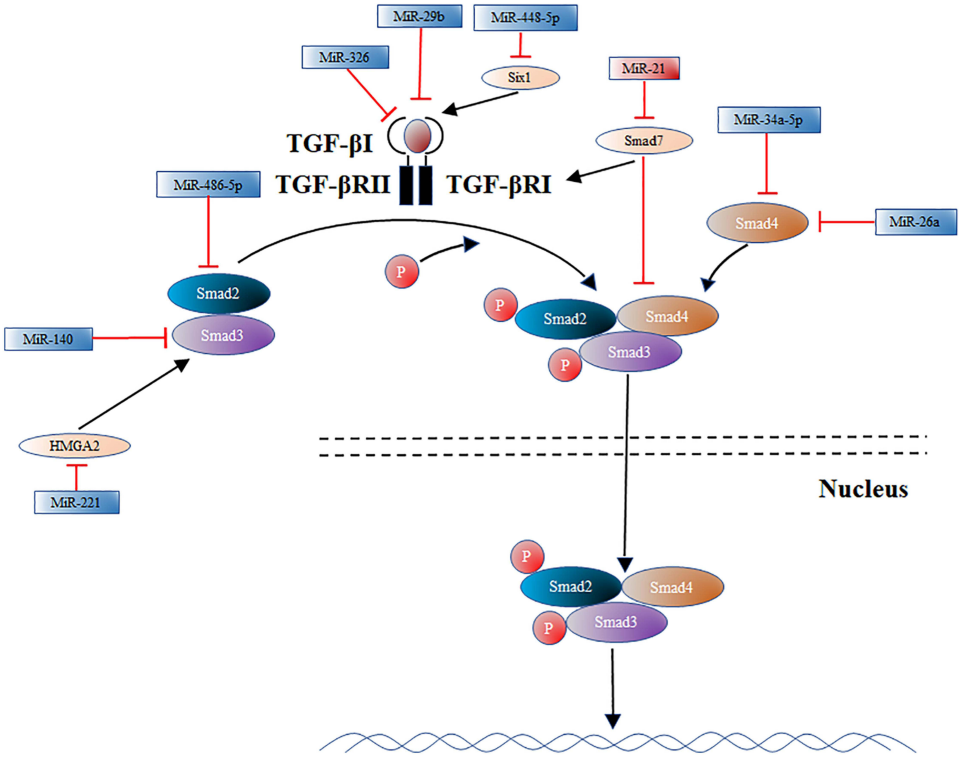

Figure 1 Targets of some miRNAs in the TGF-β/Smad signaling pathway. There are three main points in this diagram: (1) TGF-β ligands bind to heterodimeric complexes of type II and type I receptors, phosphorylating type II receptors and activating type I receptors. (2) Activated type I receptors phosphorylate Smad2 and Smad3. (3) Smad2/3 dimer forms a trimeric complex with Smad4 and translocates to the nucleus to regulate the transcription of target genes positively or negatively. (4) The targets of action of some miRNAs are also labeled in the figure, where red indicates pro-fibrotic miRNAs and blue ones indicate miRNAs that inhibit fibrosis.

BLM-induced attenuation of lung fibrosis in mice. A positive feedback loop between miR-26a and p-Smad3 in the TGF-β/Smad pathway. TGF-β1 downregulates the expression of miR-26a by promoting the phosphorylation and nuclear translocation of Smad3. This process will increase the nuclear translocation of p-Smad3 and further suppress the expression of miR-26a. Therefore, once the miR-26a/p-Smad3 loop is activated, the lung fibrosis process will be exacerbated.[18] Smad4 is a determinant of p-Smad2/Smad3 nuclear translocation. Transfection with miR-26a inhibits the expression of Smad4 and suppresses p-Smad3 nuclear translocation, which in turn inhibits the TGF-β/Smad pathway, leading to anti-fibrotic effects. Li et al[19] found that miR-26a also participates in the TGF-β2 positive feedback loop to inhibit TGF-β1 expression in human primary fetal cells. Their previous studies have found that TGF-β2 induces the release of large amounts of TGF-β1 from fibroblasts, leading to an increase in TGF-β2 levels and a positive feedback loop to promote fibrosis in an autocrine or paracrine manner.[20] MiR-26a can suppress the expression of TGF-β2, which in turn suppresses TGF-β1 levels and inhibits the fibrotic process.

In mature mouse lung tissue, miR-29b is mainly expressed in alveolar and subpleural cells at sites prone to fibrosis and in mesenchymal cells at the entrance to the alveolar ducts,[21] and downregulation of miR-29b plays an important role in pulmonary fibrosis.[22] Lian et al[22] showed that miR-29b inhibited the expression of fibroblast proliferation (MRC-5 cells and mouse embryonic fibroblasts NIH-3T3) and ECM fractions induced in silica-treated mouse lung macrophage supernatants. Tong et al[23] demonstrated in a BLM-induced mouse model of pulmonary fibrosis that astragaloside IV and ferulic acid regulate oxidative stress and TGF-β1/Smad3 signaling through miR-29b in lung tissues, resulting in a reduction of pulmonary fibrosis. Previous studies have demonstrated that the targets of miR-29b include a variety of collagen components. In the TGF-β/Smad signaling pathway-mediated collagen synthesis in pulmonary artery smooth muscle, TGF-β1 negatively regulates the expression level of miR-29b by stimulating Smad3 to interact with the miR-29b promoter, thereby promoting EMT and accelerating the fibrosis process. Moreover, miRNA-29b can inhibit TGF-β1

expression by directly targeting the 3'-UTR of TGF-β1 mRNA, thereby negatively regulating the TGF-β/Smad pathway to attenuate the EMT process and thereby delay organ fibrosis.[24]

Pais et al[25] showed that miR-140 could inhibit the TGF-β/Smad pathway by binding to Smad3 mRNA3'-UTR to directly downregulate Smad3 expression. Meanwhile, miR-140 was negatively correlated with TGF-β1 activity, and TGF-β1 could inhibit the accumulation of miR-140, forming a double negative feedback loop. It has been shown that in BLM-induced pulmonary fibrosis in mice, upregulation of miR-140 expression can have an anti-fibrotic effect through the above pathway.[26,27] Ji et al[28] discovered that MiR-486-5p expression was down-regulated in mice with silica- and bleomycin-induced pulmonary fibrosis, and the levels were also down-regulated in serum from human silicosis patients, and in lung tissues from silicosis patients and IPF patients. Their animal model also demonstrated the mechanism of action of MiR-486-5p. MiR-486-5p inhibited TGF-β1-induced fibroblast proliferation and Smad2 was a target gene of miR-486-5p. MiR-486-5p expression was downregulated and reduced the inhibition of smad2 inhibition and enhanced the TGF-β1/Smad pathway. Das et al[29] showed that miR-326 can inhibit the signaling pathway by targeting TGF-β1-3'UTR to down-regulate the expression level of TGF-β1, which in turn comes to indirectly down-regulate the phosphorylation of Smad3, thus inhibiting the signaling pathway and slowing the progression of pulmonary fibrosis. This anti-fibrotic effect of miR-326 in endometrial fibrosis was also mentioned.[30] A mouse silicosis model established in a cellular model of lung epithelial cells (A549) showed down-regulated miR-34a-5p expression in silica-induced mouse lung fibrosis assay, and Smad4 was a target of miR-34a-5p. MiR-34a-5p overexpression could inhibit the TGF-β-induced EMT process in A549 cells by acting on Smad4-3'UTR and down-regulate its expression at both mRNA and protein expression levels. In addition, this experiment revealed that transfection of Smad4 siRNA significantly increased the expression of miR-34a. Therefore, this implies that the function of miR-34a may affect EMT in lung fibrosis in vitro through some negative feedback.[31] Wang et al[32] showed that HMGA2 is a direct target of miR-221. MiR-221 over-expression inhibited the expression level of HMGA2 in adenocarcinoma A549 cells and human bronchial epithelial HBE cells, which led to the inhibition of p-smad3, the process of EMT, and the proliferation of A549 and HBE cells. Thus miR-221 could play an anti-fibrotic role, which was also verified in a BLM-induced lung fibrosis model in mice. Yang et al[33] found that miR-448-5p was downregulated in asthmatic mice and TGF-β1-treated 16HBE cells. Their experiments suggested Six1 as a target of miR-448-5p. MiR-448-5p could target the expression level of Six1 and thus inhibit TGF-β1-induced EMT and lung fibrosis.

The PI3K/Akt Signaling Pathway in Pulmonary Fibrosis

Phosphatidylinositol-3 kinases (PI3K) are a group of plasma membrane-associated lipid kinases consisting of a regulatory subunit p85 and a catalytic subunit p110 with serine/threonine (Ser/Thr) kinase activity and phosphatidylinositol kinase activity. Protein kinase B (Akt) is a Ser/Thr kinase with three isoforms, the most studied being Akt1 and Akt2, whose activation regulates downstream signaling molecules involved in the different stages of fibrosis.[34]

When the organism is stimulated, PI3K receives signals from tyrosine kinases and G protein-coupled receptors. P110 subunits bind to p85 subunits recruited near the plasma membrane, converting phosphatidylinositol 2 phosphate (PIP2) to phosphatidylinositol 3 phosphate (PIP3). PIP3 binds to Akt and translocates to the cell membrane. Akt is activated by phosphorylation of threonine and serine with the aid of phosphatidylinositol-dependent protein kinase 1 (PDK1) and phosphatidylinositol-dependent protein kinase 2 (PDK2), respectively, leading to abnormal proliferation of fibroblasts and myofibroblasts and excessive collagen deposition, thereby promoting the process of pulmonary fibrosis[35] (Figure 2).

MiR-34c-5p belongs to the miR-34 family and plays an important role in the regulation of cell proliferation and apoptosis. Pang et al[36] showed that its down-regulation of miR-34c-5p expression in a vitro model of silica interference with co-culture of HBE cells and human myeloid leukemia mononuclear (THP-1) cells. FOs-related antigen 1 (Fra-1) was a target of miR-34c-5p. The upregulation of miR-34c-5p levels was negatively correlated with Fra-1 expression. MiR-34c-5p overexpression downregulates Fra-1 expression and upregulates p53 expression, which induces PTEN to dephosphorylate PIP3 to generate PIP2, thereby negatively regulating the PI3K/Akt signaling pathway. This process promotes apoptosis, reduces cell proliferation and migration, inhibits the suppression of the EMT process, increases the expression of the epithelial marker E-cadherin, reduces the expression of the waveform protein, a-SMA, and Slug proteins, and delays the development and progression of lung fibrosis.

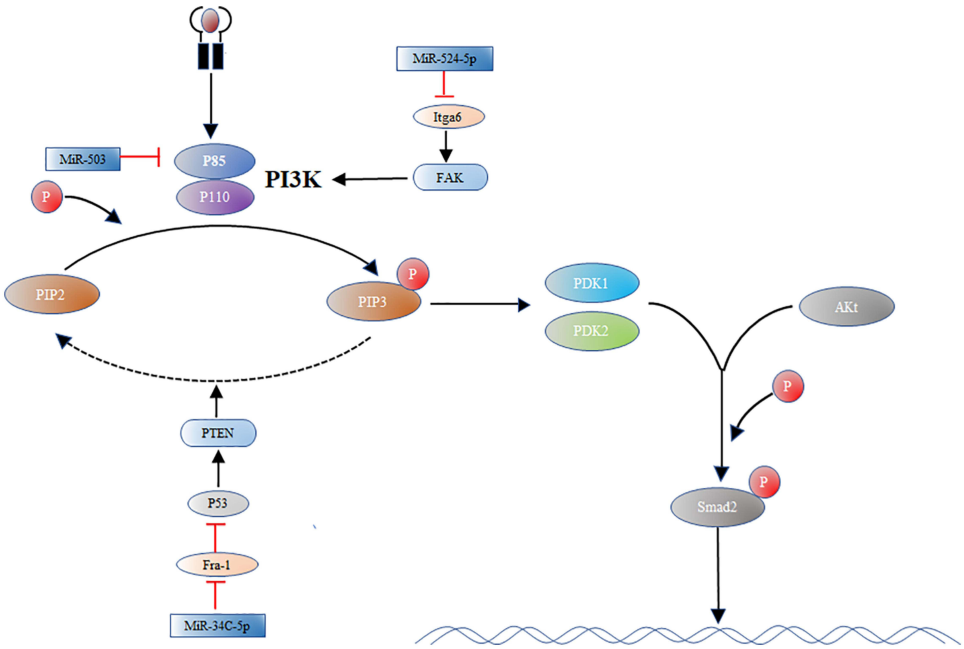

Figure 2 Targets of some miRNAs in the PI3K/Akt signaling pathway. There are three main points in this diagram: (1) PI3K receives signals from tyrosine kinases and G protein-coupled receptors. p110 subunits bind to p85 subunits recruited near the plasma membrane, converting PIP2 to PIP3. (2) PIP3 binds to Akt and translocates it to the cell membrane. (3) Akt is activated by phosphorylation of threonine and serine, respectively, with the assistance of PDK1 and PDK2. (4) The targets of action of some miRNAs are also labeled in the figure. The miRNAs involved in this signaling pathway are all antifibrotic miRNAs.

PI3K p85 is a target of miR-503 and has been validated in non-small cell lung cancer.[37] Yan et al[38] also found this in animal and cellular models of pulmonary fibrosis. They found that miR-503 expression was downregulated in silica-induced mouse lung tissues, HBE cells, and A549 cells and negatively correlated with the expression levels of activated PI3K p85 (p-PI3K p85) and PI3K p85. Upregulation of miR-503 inhibited PI3K p85, which negatively regulated the PI3K/Akt signaling pathway and decreased the expression of its downstream signaling molecules, mTOR and Snail protein. This process increases the expression level of E-calmodulin, decreases the expression level of wave protein and a-SMA, reduces the EMT process, and exerts an anti-fibrotic effect.

Integrins are a family of integrins that are cell adhesion molecules. It mediates mutual recognition and adhesion between cells and cells, and between cells and the extracellular matrix, thus transmitting extracellular signals into the cell. MiR-524-5p expression levels are significantly reduced in silica-induced lung tissue and TGF-β1- treated NIH-3T3 cells. Integrin a6 (Itga6) is a direct target of miR-524-5p and is negatively regulated by miR-524-5p.[39] Itga6 knockdown significantly inhibited FAK/PI3K/AKT phosphorylation. The upregulation of MiR-524-5p directly binds to the 3'-UTR of Itga6 and inhibits the phosphorylation of FAK, thereby negatively regulating the PI3K/AKT signaling pathway, reducing the proliferation and migration of fibroblasts, delaying alveolar structural damage, alveolar interstitial thickening and silica-induced nodule formation, and acting as an anti-fibrotic agent.

The NF-κB Signaling Pathway in Pulmonary Fibrosis

NF-κB is an important intracellular nuclear transcription factor present in almost all animal cell types. NF-κB signaling pathway is involved in an inflammatory response, immune response, regulation of apoptosis, and participation in stress response. The NF-κB family has five members, including NF-κB1 (p50), NF-κB2 (p52), RelA (p65), RelB, and c-Rel. NF-κB proteins are NF-κB1 dimeric proteins formed by the p65/p50 subunit and NF-κB2 dimeric proteins formed by the RelB/p52 subunit. NF-κB is hyperactivated in experimental mouse lung tissue, and many studies have demonstrated that inhibition of the NF-κB signaling pathway can slow down the progression of lung fibrosis.[40–43]

Classical NF-κB signaling pathway: When cells are stimulated, the ligand binds to the receptor and activates its proximal signaling bridging protein, which activates the activating IKB kinase complex IKK, which activates IKB

kinase. The activated IKB kinase phosphorylates and ubiquitinates the IKB protein, resulting in the degradation of the IKB protein and release of NF-κB dimers, which are then activated by multiple pathways and transferred to the nucleus to facilitate transcription of the target gene. Atypical NF-κB pathway: ligand and receptor binding phosphorylate the protein kinase IKKa, which in turn phosphorylates and degrades NF-κBp100 to form a p52/RelB heterodimer or NF-kB p50/RelB heterodimer that enters the nucleus to regulate transcription of target genes[44] (Figure 3).

MiR-506 expression is downregulated in lipopolysaccharide-induced rat pulmonary fibrosis model lung tissues and TGF-β1-induced MRC-5 cells, and negatively correlates with NF-κB p65 expression. The overexpression of miR-506 suppresses the expression level of p65. NF-κB p65 is a target of miR-506, which has been demonstrated in lung cancer.[45] Zhu et al[40] showed that miR-506 overexpression acts directly on the 3'-UTR of NF-κB p65, downregulates the expression level of p65 subunit and inhibits the expression level of the NF-κB signaling pathway. This process decreases the expression level of lung fibrosis-related proteins, delays the EMT process, and acts as an anti-fibrotic agent. Meanwhile, miR-506 induces apoptosis in vivo and in vitro by inhibiting the expression of p65, inhibits the production of inflammatory factors, suppresses the inflammatory response in the lung, and improves the extent of lung injury and fibrosis.

Extracellular high mobility group frame protein 1 (HMGB1) is a multifunctional cytokine involved in the processes of infection, inflammation, apoptosis, and immune response by binding to specific cell surface receptors.[46–49] RAGE is a transmembrane receptor of the immunoglobulin superfamily that interacts with ligands upon activation of proinflammatory and immune responses. RAGE regulates the activation of the NF-κB signaling pathway.[50] HMGB1 induces lung fibrosis by promoting the release of TGF-β1 and the expression of α-SMA and collagen I through the RAGE/NF-κB signaling pathway. MiR-627 is downregulated in vitro model of human lung tissue cells and negatively regulates the

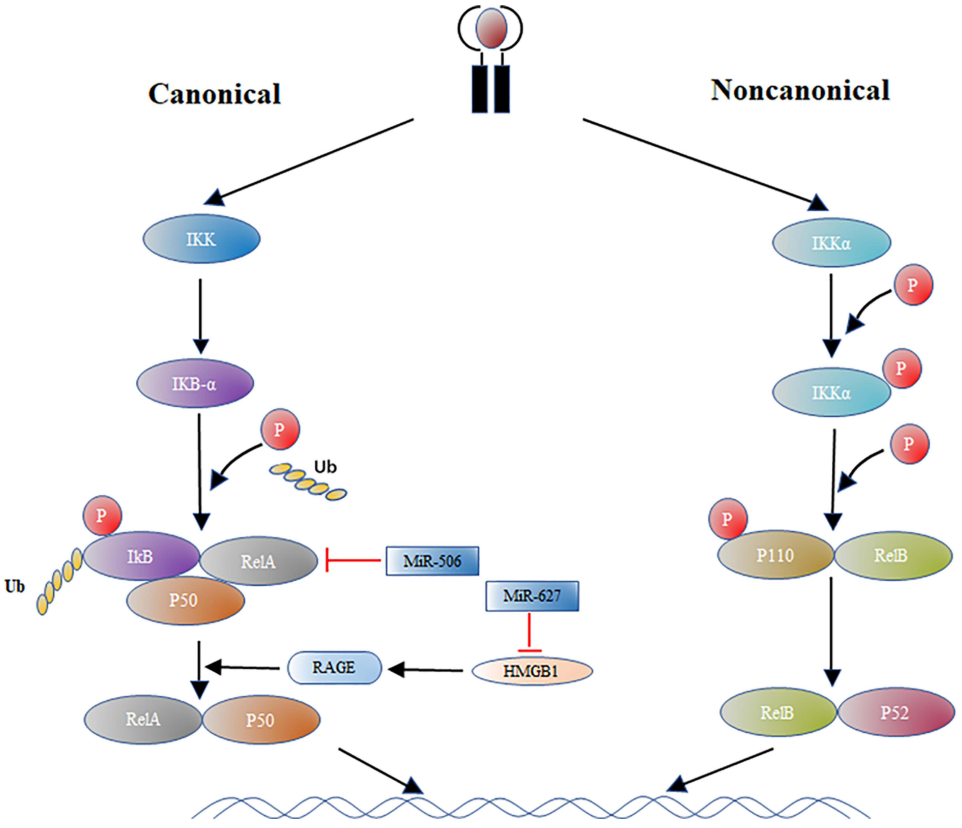

Figure 3 Targets of some miRNAs in the Classical and Atypical NF-κB pathways. (1) Classical NF-κB pathway: The ligand binds to the receptor and activates its proximal signaling bridging protein, which activates the activating IKB kinase complex IKK, which activates IKB kinase. The activated IKB kinase phosphorylates and ubiquitinates the IKB protein, resulting in the degradation of the IKB protein and release of NF-κB dimers. (2) Atypical NF-κB pathway: Ligand and receptor binding phosphorylate the protein kinase IKKa, which in turn phosphorylates and degrades NF-κBp100 to form a p52/RelB heterodimer or NF-kB p50/RelB heterodimer that enters the nucleus to regulate the transcription of target genes. (3) Both miRNAs involved in this signaling pathway play anti-fibrotic roles and have been labeled in figure.

expression level of HMGB1. MiR-627 directly binds to the 3'-untranslated region of HMGB1 and inhibits its expression, thereby suppressing the activation of the RAGE/NF-κB signaling pathway and the release of TGF-β1.[43] This process partially reverses TGF-β1-induced fibroblast proliferation and lung fibrosis-related protein expression, thereby inhibiting the lung fibrosis process.

Other Signaling Pathways

The Wnt signaling pathway, Hedgehog signaling pathway, Notch signaling pathway, and other signaling pathways were found to be involved in the regulation of pulmonary fibrosis.[51–54] Shi et al[51] reported that miR-140 expression was decreased in lung tissues of BLM-induced pulmonary fibrosis in mice, while osteoglycin (OGN) expression was up-regulated, and OGN was found to be a target of MiR-140 by software analysis. MiR-140 specifically binds to OGN-3'-UTR and downregulates OGN gene expression, thereby inhibiting lung fibroblast proliferation and promoting lung fibroblast apoptosis. This process, in turn, activates the Wnt signaling pathway, which inhibits the expression of lung fibrosis-related factors and hence prevents the progression of lung fibrosis in ILD mice. A recent study demonstrated that Wnt3a is a target gene of miR-27a-3p and is negatively regulated in MRC-5 cells. MiR-27a-3p reduced the inhibition of ubiquitination degradation of β-catenin by Wnt3a and inhibited the nuclear translocation of β-catenin, which resulted in the down-regulation of the expression of collagen type I and type III in MRC-5 cells.[55] Zhuang et al[53] found that miR-338 expression was downregulated in BLM-induced pulmonary fibrosis in mice. Smoothened (SMO), a key activator of the Hedgehog signaling pathway, is a direct target of miR-338. Up-regulation of MiR-338 expression levels negatively regulates SMO, thereby inhibiting the Hedgehog signaling pathway, reducing the EMT process, and delaying the development of lung fibrosis. Zhao et al[54] found that miR-30d was down-regulated in TGF-β1-treated human lung fibroblast (NHLF) and negatively regulated the expression of JAG1, the ligand of Notch. MiR-30d directly combines with the 3'-UTR of JAG1 to inhibit JAG1 mRNA expression and protein levels, which blocks the Notch signaling pathway to inhibit the TGF-β1-induced lung fibrosis process (Figure 4).

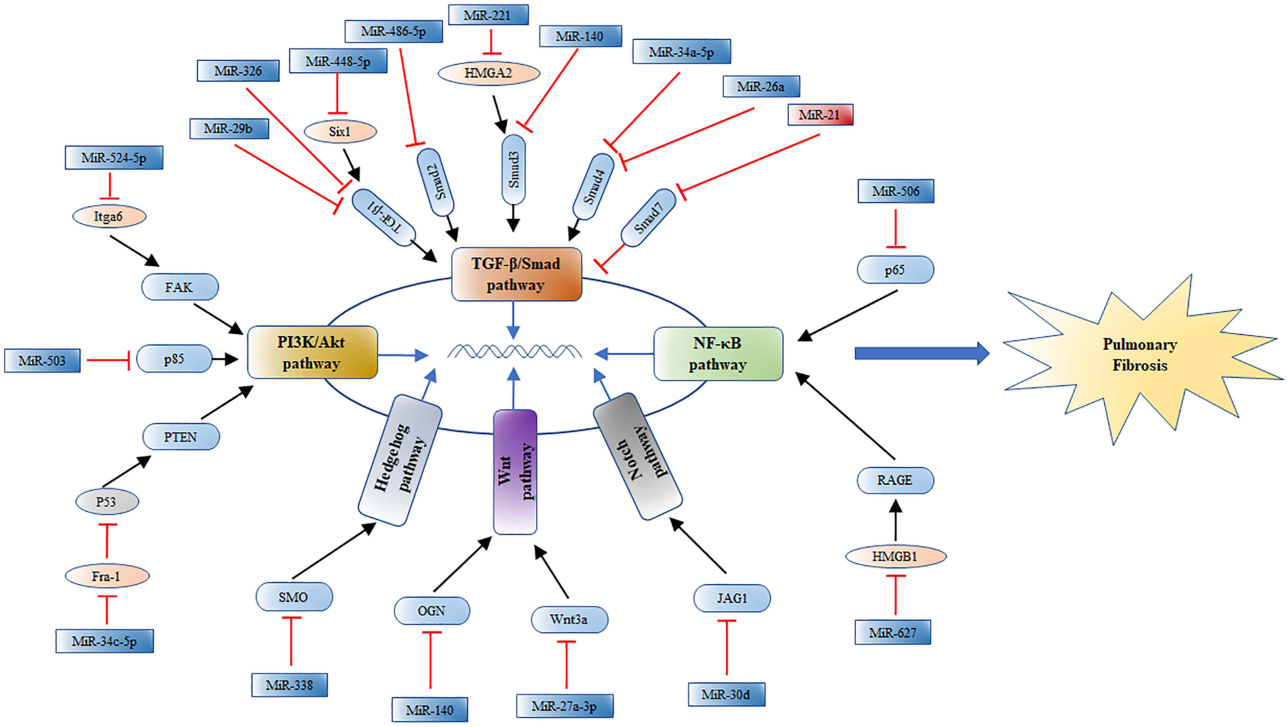

Figure 4 A diagram summarizes the targets of the miRNAs mentioned in this paper in different signaling pathways.

LncRNA in the Signaling Pathway of Pulmonary Fibrosis

LncRNAs are ncRNAs greater than 200 nucleotides in length. They regulate gene expression in multiple ways at the epigenetic, chromatin remodeling, transcriptional and translational levels.[5,56,57] LncRNAs are time-specific and tissue-specific, and their transcription can act as signaling molecules to further regulate the expression of other genes. Some of them can work as competitive endogenous RNAs (ceRNAs) to adsorb certain specific miRNAs,[57,58] thereby regulating the expression of miRNAs target genes and thus the process of pulmonary fibrosis. The following are some of the lncRNAs and corresponding miRNAs that have been relatively well studied to play a ceRNA role in the pulmonary fibrosis signaling pathway (Table 2).

NEAT1 is a non-coding RNA about 3.2 kb long, which is mainly enriched in the nucleus and is a key non-coding RNA for the formation and maintenance of the nuclear substructure paraspeckle. Zhang et al[59] showed that the expression levels of NEAT1 and miR-9-5p were negatively correlated in PF tissues and TGF-β1-induced cells. NEAT1 was significantly upregulated, whereas miR-9-5p was downregulated. NEAT1 directly targets miR-9-5p and regulates TGF-β1-induced PF. The expression of E-calmodulin was increased, while the expression of N-calmodulin, waveform protein, collagen I, collagen III and α-SMA was decreased. MiR-9-5p overexpression inhibited the expression of TGF-β1 and p-Smad2, while NEAT1 overexpression attenuated this effect. Furthermore, after BLM treatment, NEAT1 inhibition enhanced E-calmodulin expression and decreased TGF-β1, p-Smad2, N-calmodulin, collagen I, collagen III, α-SMA and vimentin expression. Overall, NEAT1 knockdown inhibited EMT by regulating miR-9-5p and TGF-β signaling, thereby attenuating PF.

In lung tissue from IPF patients and in TGF-β1-induced HBE and A549 cells, H19 expression was negatively correlated with miR-140 expression. As we have mentioned before, miR-140 plays an anti-fibrotic role in the TGF-β/Smad3 pathway.[25] Animal experiments showed that H19 knockdown attenuated BLM-induced lung fibrosis in mice. H19 acts by binding to miR-140 to reduce the expression of miR-140. MiR-140 increase inhibited TGF-β1-induced lung fibrosis, and H19 upregulation attenuated the inhibitory effect of miR-140 on TGF-β1-induced lung fibrosis, which is involved in the TGF-β /Smad3 pathway.[27] Taken together, H19 knockdown attenuated pulmonary fibrosis through the regulatory network of the lncRNA H19/miR-140/TGF-β/Smad3 signaling pathway.

The lncRNA-SNHG6 (small nucleolar RNA host gene 6) is located in the chromosome 8q13.1 region and is involved in the induction of proliferation, migration and EMT processes in a variety of cancers.[60] Deng et al[61] found that SNHG6 also plays a role in the lung fibrosis signaling pathway. SNHG6 overexpression induced collagen accumulation in fibroblasts and fibroblast activation in primary lung fibroblasts after BLM treatment. As we mentioned earlier, miR-26a plays a protective role in the lung fiber TGF-β1/Smads signaling pathway.[18] SNHG6 negatively regulates miR-26a-5p, and thus promotes the lung fibrosis process. Silencing SNHG6 significantly attenuated TGF-β1-induced expression of fibrosis markers, cell proliferation, migration, and differentiation, and increased nuclear translocation of p-Smad2/3 by regulating miR-26a-5p expression in mouse lung fibroblasts. That is, silencing of lncRNA SNHG6 attenuated BLM-induced lung fibrosis in mice via miR-26a-5p/TGF-β1/smads axis.

Table 2 Sponging Effect of lncRNAs on Target miRNAs in Pulmonary Fibrosis Signaling Pathway

LncRNAs	Signaling Pathways	Expression	Effect	Target
NEAT1	TGF-β/Smad	Increase	Pro-fibrotic	MiR-9-5p
H19	TGF-β/Smad	Increase	Pro-fibrotic	MiR-140
SNHG6	TGF-β/Smad	Increase	Pro-fibrotic	MiR-26a-5p
Hoxaas3	TGF-β/Smad	Increase	Pro-fibrotic	MiR-450b-5p
Lnc556	TGF-β1-smad/p38MAPK	Increase	Pro-fibrotic	MiR-29b-2-5p
Lnc865	TGF-β1-smad/p38MAPK	Increase	Pro-fibrotic	MiR-29b-2-5p
MALAT1	PI3K/Akt/mTOR/Snail	Increase	Pro-fibrotic	MiR-503
SNHG16	Notch	Increase	Pro-fibrotic	MiR-455-3p

The small house mouse Hoxa cluster antisense RNA 3 (Hoxaas3) belongs to the Hox gene cluster that regulates embryonic development, hematopoietic lineage and differentiation and is a group of highly homologous transcription factors.[62] In IPF patient lung tissues and BLM-treated mouse lung tissues, Hoxaas3 expression is elevated while miR-450b-5p expression is decreased. In TGF-β1-treated mouse lung fibroblasts, Hoxaas3 can regulate lung fibroblast activation and fibrogenesis by acting as a ceRNA for miR-450b-5p. At the same time, upregulation of miR-450b-5p suppressed the Hoxaas3-induced increase in fibronectin, waveform protein and a-SMA. In this process, miR-450b-5p directly represses runt-related transcription factor 1 (Runx1) in a transcriptional manner, while Runx1 inhibition attenuates the pro-fibrotic effects of Hoxaas3. In addition, Hoxaas3 is regulated by the TGF-β1/Smad4 pathway as its transcriptional target. In summary, Hoxaas3, as a downstream signal of TGF-β1/Smad4, decreases miR-450b-5p expression to stimulate Runx1 levels and activity to induce the fibrotic process.[63]

NONMMUT039556 (Lnc556) and NONMMUT039865 (Lnc865) are significantly upregulated in BLM-induced pulmonary fibrosis. MiR-29b-2-5p is their common target, which has been previously demonstrated.[64] Among the lung fibrosis signaling pathways involved in lnc556 and lnc865, the upstream pathway is TGF-β1-smad2/3 and p38MAPK, and the downstream pathway is Kruppel like factor 4 (KLF4). Shen et al[65] showed that acetyl oxygen benzoate engeletin ester (AOBEE) inhibits lnc865/lnc556-miR-29b-2-5p-STAT3 axis through TGFβ1-smad2/3 and p38MAPK signaling pathways, promotes KLF4 degradation, and blocks fibroblasts to myofibroblasts differentiation, myofibroblasts proliferation and extracellular matrix deposition. This study also confirmed that lnc556 and lnc865 negatively regulated anti-fibrotic miR-29b-2-5p and promoted pulmonary fibrosis.

In the previous section on miRNA targets in the lung fibrosis signaling pathway, we have already mentioned that miR-503 plays an anti-fibrotic role and one of its targets is PI3K p85.[38] In silica-induced lung fibrosis in mice, the lncRNA Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) expression level is upregulated in silica-treated HBE cells, and it acts as a ceRNA that binds directly to miR-503 and inhibits miR-503 expression, thus triggering the PI3K/Akt/mTOR/Snail pathway and acting as a pro-fibrotic agent.[38]

Liu et al[66] showed that the expression of SNHG16 was significantly elevated in BLM-induced mouse lung fibrosis and TGF-β-treated mouse lung fibroblasts, and knockdown of SNHG16 inhibited the fibrotic process. Anti-fibrosis MiR-455-3p was negatively correlated with the expression of SNHG16 and was a target of SNHG16. Meanwhile, otch2 in the Notch family is also a target of miR-455-3p. Meanwhile, it was found that SNHG16 could act as a sponge for miR-455-3p, thus regulating the expression process of Notch2 by binding miR-455-3p.

CircRNA in the Signaling Pathway of Pulmonary Fibrosis

Compared with the depth of research on miRNA and lncRNA, circRNA has only been studied in recent years. Currently, studies on circRNA in pulmonary fibrosis is still lacking. CircRNAs are a class of covalently closed, cyclic, endogenous non-coding RNAs without a 5′-end cap and a 3′-end polyadenylate tail. They are not affected by RNA exonucleases and are more stably expressed and less susceptible to degradation. CircRNAs are involved in regulating gene transcription and splicing, mediating protein-protein interactions, and inhibiting ribosomal RNA maturation. Additionally, circRNAs can also serve as ceRNAs to competitively bind specific miRNAs and regulate the expression of target genes.[67] Since the study of circRNAs in the classical signaling pathway of pulmonary fibrosis is not very clear, some circRNAs that have been defined targets are mainly listed below (Table 3).

Table 3 Sponging Effect of circRNAs on Target miRNAs in Pulmonary Fibrosis

CircRNAs	Expression	Effect	Target
circTADA2A	Decrease	Anti-fibrotic	MiR-526b MiR-203
circCDR1as	Increase	Pro-fibrotic	MiR-7
circ0044226	Increase	Pro-fibrotic	MiR-7
circHIPK3	Increase	Pro-fibrotic	MiR-30a-3p MiR-338-3p
circRNA0026344	Decrease	Anti-fibrotic	MiR-21

Li et al[68] found that circTADA2A was downregulated in both IPF primary human lung fibroblasts and human IPF fibroblast cell lines. CircTADA2A inhibited lung fibroblast activation via miR-526b/Cav1 and reduced lung fibroblast proliferation via miR-203/Cav2, thereby inhibiting excessive ECM deposition and alleviating IPF. Yao et al[69] showed that circCDR1as expression was upregulated in an animal model of silica-induced pulmonary fibrosis, and it could promote the formation of pulmonary fibrosis by competitively binding miR-7, boosting the expression of TGFBR2 protein and initiating EMT. Zhang et al[70] found that circ0044226 was increased and miR-7 was decreased in myofibroblasts derived from IPF mouse model and fibroblast-to-myofibroblast transformation (FMT). MiR-7 was the target of circ0044226 and sp1 was the target of miR-7. Circ0044226 acted as miR-7 sponge to positively regulate the expression of sp1. Xu et al[71] showed that circHIPK3 could enhance the expression of FOXK2, a driver transcription factor of glycolysis, by sponging miR-30a-3p, thereby promoting fibroblast glycolysis and activation. Zhang et al[72] identified that miR-338-3p is also a target of circHIPK3. circHIPK3 regulates FMT by acting as an endogenous miR-338-3p sponge and inhibiting miR-338-3p activity, leading to increased expression of SOX4 and COL1A1. Circ0026344 expression is declined in cigarette smoke (CS)- treated HBE cells. Circ0026344 acts as a miRNA sponge for miR-21. Downregulation of circ0026344 in CS-induced bronchial epithelial cells increases miR-21 levels. Elevated miR-21 is transported to bronchial fibroblasts via exosomes and then targeted to inhibit Smad7 to activate the TGF-β1/Smads pathway.[73] The activated signaling pathway induces bronchial fibroblast differentiation and ECM deposition, leading to PF.

Conclusion

In summary, many ncRNAs are reported to be involved in the lung fibrosis process of animal or cell models, which act as pro-fibrotic or anti-fibrotic agents through different signaling pathways. The same ncRNA can also act on different targets and participate in different signaling pathways. If ncRNAs or their targets can be specifically regulated, the progression of pulmonary fibrosis can be slowed down. At the same time, if specific ncRNAs can be identified, it can also provide new ideas for early clinical diagnosis of pulmonary fibrosis. However, the pulmonary fibrosis process is not regulated by a single signaling pathway, but by multiple signals which can interact to form a complex signaling network that together regulates the pulmonary fibrosis process. The process is very complex. There are many signaling pathways and mechanisms of action that have not yet been fully elucidated. The mechanism of action of many ncRNAs was demonstrated in vitro experiments but has still not been validated in human pulmonary fibrosis lung tissue, which is still a direction we need to investigate.

Data Sharing Statement

No datasets have been used in producting this work.

Author Contributions

All authors have made significant contributions to the reported work, whether in conceptualization, study design, execution, data acquisition, analysis, and interpretation, or all of these; participated in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article will be submitted; and have agreed to take responsibility for all aspects of the work.

Funding

This work was supported by Norman Bethune Program of Jilin University (Grant No. 2022B14), "13th five-year plan" Science and Technology Research Project of Jilin Provincial Department of Education (Grant No. JJKH20190048KJ), the Youth Science and Technology Backbone Training Program of Health Commission of Jilin Province (Grant No. 2019Q003), as well as the Medical and Health Talent Special Project of Jilin Province - National Natural Science Foundation of China Cultivation Project (Grant No. 2019SRCJ013).

Disclosure

The authors have no conflicts of interest to declare.

References

1. Fang Y, Tian J, Fan Y, Cao P. Latest progress on the molecular mechanisms of idiopathic pulmonary fibrosis. *Mol Biol Repo*. 2020;47(12):9811–9820. doi:10.1007/s11033-020-06000-6
2. Wuyts WA, Wijsenbeek M, Bondue B, et al. Idiopathic pulmonary fibrosis: best practice in monitoring and managing a relentless fibrotic disease. *Respiration*. 2020;99(1):73–82. doi:10.1159/000504763
3. Kass DJ, Kaminski N. Evolving genomic approaches to idiopathic pulmonary fibrosis: moving beyond genes. *Clin Transl Sci*. 2011;4(5):372–379. doi:10.1111/j.1752-8062.2011.00287.x
4. Cui H, Xie N, Thannickal VJ, Liu G. The code of non-coding RNAs in lung fibrosis. *Cell Mol Life Sci*. 2015;72(18):3507–3519. doi:10.1007/s00018-015-1939-6
5. Wilusz JE, Sunwoo H, Spector DL. Long noncoding RNAs: functional surprises from the RNA world. *Genes Dev*. 2009;23(13):1494–1504. doi:10.1101/gad.1800909
6. Ali Syeda Z, Langden SSS, Munkhzul C, Lee M, Song SJ. Regulatory mechanism of microRNA expression in cancer. *Int J Mol Sci*. 2020;21(5). doi:10.3390/ijms21051723
7. Gebert LFR, MacRae IJ. Regulation of microRNA function in animals. *Nat Rev Mol Cell Biol*. 2019;20(1):21–37. doi:10.1038/s41580-018-0045-7
8. Liu G, Friggeri A, Yang Y, et al. MiR-21 mediates fibrogenic activation of pulmonary fibroblasts and lung fibrosis. *J Exp Med*. 2010;207(8):1589–1597. doi:10.1084/jem.20100035
9. Li S, Zhao J, Shang D, Kass DJ, Zhao Y. Ubiquitination and deubiquitination emerge as players in idiopathic pulmonary fibrosis pathogenesis and treatment. *JCI Insight*. 2018;3(10). doi:10.1172/jci.insight.120362
10. Scotton CJ, Chambers RC. Molecular targets in pulmonary fibrosis: the myofibroblast in focus. *Chest*. 2007;132(4):1311–1321. doi:10.1378/chest.06-2568
11. Fernandez IE, Eickelberg O. New cellular and molecular mechanisms of lung injury and fibrosis in idiopathic pulmonary fibrosis. *Lancet*. 2012;380(9842):680–688. doi:10.1016/S0140-6736(12)61144-1
12. Hewlett JC, Kropski JA, Blackwell TS. Idiopathic pulmonary fibrosis: epithelial-mesenchymal interactions and emerging therapeutic targets. *Matrix Biol*. 2018;71-72:112–127. doi:10.1016/j.matbio.2018.03.021
13. Fernandez IE, Eickelberg O. The impact of TGF-beta on lung fibrosis: from targeting to biomarkers. *Proc Am Thorac Soc*. 2012;9(3):111–116. doi:10.1513/pats.201203-023AW
14. Saito S, Deskin B, Rehan M, et al. Novel mediators of idiopathic pulmonary fibrosis. *Clin Sci*. 2022;136(16):1229–1240. doi:10.1042/CS20210878
15. Zhou J, Xu Q, Zhang Q, Wang Z, Guan S. A novel molecular mechanism of microRNA-21 inducing pulmonary fibrosis and human pulmonary fibroblast extracellular matrix through transforming growth factor beta1-mediated SMADs activation. *J Cell Biochem*. 2018;119(9):7834–7843. doi:10.1002/jcb.27185
16. Tzavlaki K, Moustakas A. TGF-beta Signaling. *Biomolecules*. 2020;10(3). doi:10.3390/biom10030487
17. Hata A, Chen Y. TGF-beta signaling from receptors to Smads. *Cold Spring Harbor Perspect Biol*. 2016;8(9). doi:10.1101/cshperspect.a022061
18. Liang H, Xu C, Pan Z, et al. The antifibrotic effects and mechanisms of microRNA-26a action in idiopathic pulmonary fibrosis. *Mol Ther*. 2014;22(6):1122–1133. doi:10.1038/mt.2014.42
19. Li X, Liu L, Shen Y, et al. MicroRNA-26a modulates transforming growth factor beta-1-induced proliferation in human fetal lung fibroblasts. *Biochem Biophys Res Commun*. 2014;454(4):512–517. doi:10.1016/j.bbrc.2014.10.106
20. Wen F, Kohyama T, Sköld CM, et al. Glucocorticoids modulate TGF-β production by human fetal lung fibroblasts. *Inflammation*. 2003;27:9–19. doi:10.1023/a:1022683010976
21. Cushing L, Kuang PP, Qian J, et al. MiR-29 is a major regulator of genes associated with pulmonary fibrosis. *Am J Respir Cell Mol Biol*. 2011;45(2):287–294. doi:10.1165/rcmb.2010-0323OC
22. Lian X, Chen X, Sun J, et al. MicroRNA-29b inhibits supernatants from silica-treated macrophages from inducing extracellular matrix synthesis in lung fibroblasts. *Toxicol Res*. 2017;6(6):878–888. doi:10.1039/c7tx00126f
23. Tong J, Wu Z, Wang Y, et al. Astragaloside IV synergizing with ferulic acid ameliorates pulmonary fibrosis by TGF-β1/Smad3 signaling. *Evid Based Complement Alternat Med*. 2021;2021:8845798. doi:10.1155/2021/8845798
24. Wang T, Li Y, Chen J, Xie L, Xiao T. TGF-β1/Smad3 signaling promotes collagen synthesis in pulmonary artery smooth muscle by down-regulating miR-29b. *Int J Clin Exp Pathol*. 2018;11:5592–5601
25. Pais H, Nicolas FE, Soond SM, et al. Analyzing mRNA expression identifies Smad3 as a microRNA-140 target regulated only at protein level. *RNA*. 2010;16(3):489–494. doi:10.1261/rna.1701210
26. Wang C, Song X, Li Y, et al. Low-dose paclitaxel ameliorates pulmonary fibrosis by suppressing TGF-beta1/Smad3 pathway via miR-140 upregulation. *PLoS One*. 2013;8(8). doi:10.1371/journal.pone.0070725
27. Wang X, Cheng Z, Dai L, et al. Knockdown of long noncoding RNA H19 represses the progress of pulmonary fibrosis through the transforming growth factor β/Smad3 pathway by regulating microRNA 140. *Mol Cell Biol*. 2019;39(12). doi:10.1128/MCB.00143-19
28. Ji X, Wu B, Fan J, et al. The anti-fibrotic effects and mechanisms of microRNA-486-5p in pulmonary fibrosis. *Sci Rep*. 2015;5:14131. doi:10.1038/srep14131
29. Das S, Kumar M, Negi V, et al. MicroRNA-326 regulates profibrotic functions of transforming growth factor-beta in pulmonary fibrosis. *Am J Respir Cell Mol Biol*. 2014;50(5):882–892. doi:10.1165/rcmb.2013-0195OC
30. Ning J, Zhang H, Yang H. MicroRNA-326 inhibits endometrial fibrosis by regulating TGF-beta1/Smad3 pathway in intrauterine adhesions. *Mol Med Rep*. 2018;18(2):2286–2292. doi:10.3892/mmr.2018.9187
31. Qi Y, Zhao A, Yang P, Jin L, Hao C. MiR-34a-5p Attenuates EMT through targeting SMAD4 in silica-induced pulmonary fibrosis. *J Cell Mol Med*. 2020;24(20):12219–12224. doi:10.1111/jcmm.15853
32. Wang Y, Liu J, Tang H, et al. MiR-221 targets HMGA2 to inhibit bleomycin-induced pulmonary fibrosis by regulating TGF-beta1/Smad3-induced EMT. *Int J Mol Med*. 2016;38(4):1208–1216. doi:10.3892/ijmm.2016.2705
33. Yang Z, Qu Z, Yi M, et al. MiR-448-5p inhibits TGF-beta1-induced epithelial-mesenchymal transition and pulmonary fibrosis by targeting Six1 in asthma. *J Cell Physiol*. 2019;234(6):8804–8814. doi:10.1002/jcp.27540

34. Saito S, Zhuang Y, Shan B, et al. Tubastatin ameliorates pulmonary fibrosis by targeting the TGFbeta-PI3K-Akt pathway. *PLoS One*. 2017;12(10): e0186615. doi:10.1371/journal.pone.0186615
35. Wang J, Hu K, Cai X, et al. Targeting PI3K/AKT signaling for treatment of idiopathic pulmonary fibrosis. *Acta Pharmaceutica Sinica B*. 2022;12 (1):18–32. doi:10.1016/j.apsb.2021.07.023
36. Pang X, Shi H, Chen X, et al. MiRNA-34c-5p targets Fra-1 to inhibit pulmonary fibrosis induced by silica through p53 and PTEN/PI3K/Akt signaling pathway. *Environ Toxicol*. 2022;37(8):2019–2032. doi:10.1002/tox.23547
37. Yang Y, Liu L, Zhang Y, et al. MiR-503 targets PI3K p85 and IKK-beta and suppresses progression of non-small cell lung cancer. *Int J Cancer*. 2014;135(7):1531–1542. doi:10.1002/ijc.28799
38. Yan W, Wu Q, Yao W, et al. MiR-503 modulates epithelial-mesenchymal transition in silica-induced pulmonary fibrosis by targeting PI3K p85 and is sponged by lncRNA MALAT1. *Sci Rep*. 2017;7(1):11313. doi:10.1038/s41598-017-11904-8
39. Yuan J, Li P, Pan H, et al. MiR-542-5p attenuates fibroblast activation by targeting integrin alpha6 in silica-induced pulmonary fibrosis. *Int J Mol Sci*. 2018;19(12). doi:10.3390/ijms19123717
40. Zhu M, An Y, Zhang X, Wang Z, Duan H. Experimental pulmonary fibrosis was suppressed by microRNA-506 through NF-kappa-mediated apoptosis and inflammation. *Cell Tissue Res*. 2019;378(2):255–265. doi:10.1007/s00441-019-03054-2
41. Xie B, Lu C, Chen C, Zhou J, Deng Z. MiR-135a alleviates silica-induced pulmonary fibrosis by targeting NF-kappaB/inflammatory signaling pathway. *Mediators Inflammat*. 2020;2020. doi:10.1155/2020/1231243
42. Xiao K, He W, Guan W, et al. Mesenchymal stem cells reverse EMT process through blocking the activation of NF-kappaB and Hedgehog pathways in LPS-induced acute lung injury. *Cell Death Dis*. 2020;11(10):863. doi:10.1038/s41419-020-03034-3
43. Li J, Kong X, Jiang S, et al. MiR-627/HMGB1/NF-kappaB regulatory loop modulates TGF-beta1-induced pulmonary fibrosis. *J Cell Biochem*. 2019;120(3):2983–2993. doi:10.1002/jcb.27038
44. Alharbi KS, Fuloria NK, Fuloria S, et al. Nuclear factor-kappa B and its role in inflammatory lung disease. *Chem Biol Interact*. 2021;345. doi:10.1016/j.cbi.2021.109568
45. Yin M, Ren X, Zhang X, et al. Selective killing of lung cancer cells by miRNA-506 molecule through inhibiting NF-kappaB p65 to evoke reactive oxygen species generation and p53 activation. *Oncogene*. 2015;34(6):691–703. doi:10.1038/onc.2013.597
46. Laws TR, Clark GC, D'Elia RV. Immune profiling of the progression of a BALB/c mouse aerosol infection by Burkholderia pseudomallei and the therapeutic implications of targeting HMGB1. *Int J Infect Dis*. 2015;40:1–8. doi:10.1016/j.ijid.2015.09.003
47. Qi L, Sun X, Li FE, et al. HMGB1 promotes mitochondrial dysfunction-triggered striatal neurodegeneration via autophagy and apoptosis activation. *PLoS One*. 2015;10(11):e0142901. doi:10.1371/journal.pone.0142901
48. Tabata C, Kanemura S, Tabata R, et al. Serum HMGB1 as a diagnostic marker for malignant peritoneal mesothelioma. *J Clin Gastroenterol*. 2013;47(8):684–688. doi:10.1097/MCG.0b013e318297fa65
49. Tabata C, Terada T, Tabata R, et al. Serum thioredoxin-1 as a diagnostic marker for malignant peritoneal mesothelioma. *J Clin Gastroenterol*. 2013;47(1):e7–e11. doi:10.1097/MCG.0b013e31824e901b
50. Xie Y, Yu N, Chen Y, Zhang K, Ma HY, Di Q. HMGB1 regulates P-glycoprotein expression in status epilepticus rat brains via the RAGE/ NF-kappaB signaling pathway. *Mol Med Rep*. 2017;16(2):1691–1700. doi:10.3892/mmr.2017.6772
51. Shi S, Li H. Overexpressed microRNA-140 inhibits pulmonary fibrosis in interstitial lung disease via the Wnt signaling pathway by downregulating osteoglycin. *Am J Physiol Cell Physiol*. 2020;319(5):C895–C905. doi:10.1152/ajpcell.00479.2019
52. Henderson J, Wilkinson S, Przyborski S, Stratton R, O'Reilly S. MicroRNA27a-3p mediates reduction of the Wnt antagonist sFRP-1 in systemic sclerosis. *Epigenetics*. 2021;16(7):808–817. doi:10.1080/15592294.2020.1827715
53. Zhuang Y, Dai J, Wang Y, et al. MiR-338*targeting smoothened to inhibit pulmonary fibrosis by epithelial-mesenchymal transition. *Am J Transl Res*. 2016;8:3206–3213
54. Zhao S, Xiao X, Sun S, et al. MicroRNA-30d/JAG1 axis modulates pulmonary fibrosis through Notch signaling pathway. *Pathol Res Pract*. 2018;214(9):1315–1323. doi:10.1016/j.prp.2018.02.014
55. Li-jing L, Hong Q, Ke H, Zizhen Z, Jian-bin H. MiR-27a-3p inhibited synthesis of Col I and Col III in pulmonary fibroblasts through Wnt3a/β-catenin signaling pathway (in Chinese). *CPB*. 2019;35(02):229–234
56. Wang W, Min L, Qiu X, et al. Biological function of long non-coding RNA (LncRNA) xist. *Front Cell Develop Biol*. 2021;9:645–647. doi:10.3389/ fcell.2021.645647
57. Jiang H, Chen Y, Yu T, et al. Inhibition of lncRNA PFRL prevents pulmonary fibrosis by disrupting the miR-26a/smad2 loop. *Am J Physiol Lung Cell Mol Physiol*. 2018;315(4):563–575. doi:10.1152/ajplung.00434.2017
58. Huang R, Bai C, Liu X, et al. The p53/RMRP/miR122 signaling loop promotes epithelial-mesenchymal transition during the development of silica-induced lung fibrosis by activating the notch pathway. *Chemosphere*. 2021;263:128–133. doi:10.1016/j.chemosphere.2020.128133
59. Zhang Y, Yao X, Wu Y, Cao G, Han D. LncRNA NEAT1 regulates pulmonary fibrosis through miR-9-5p and TGF-β signaling pathway. *Eur Rev Med Pharmacol Sci*. 2020;24(16):8483–8492
60. Khan K, Irfan M, Sattar AA, et al. LncRNA SNHG6 role in clinicopathological parameters in cancers. *Eur J Med Res*. 2023;28(1):363. doi:10.1186/s40001-023-01358-2
61. Deng W, Zhang Y, Fang P, Shi H, Yang S. Silencing lncRNA Snhg6 mitigates bleomycin-induced pulmonary fibrosis in mice via miR-26a-5p/TGF-beta1-smads axis. *Environ Toxicol*. 2022;37(10):2375–2387. doi:10.1002/tox.23603
62. Saurin AJ, Delfini MC, Maurel-Zaffran C, Graba Y. The generic facet of hox protein function: (Trends in Genetics 34, 941–953, 2018). *Trends Genet*. 2019;35(4):316. doi:10.1016/j.tig.2018.11.006
63. Lin S, Zhang R, Xu L, et al. LncRNA Hoxaas3 promotes lung fibroblast activation and fibrosis by targeting miR-450b-5p to regulate Runx1. *Cell Death Dis*. 2020;11(8):706. doi:10.1038/s41419-020-02889-w
64. Li C, Wang Z, Zhang J, et al. Crosstalk of mRNA, miRNA, lncRNA, and circRNA and their regulatory pattern in pulmonary fibrosis. *Mol Ther Nucleic Acids*. 2019;18:204–218. doi:10.1016/j.omtn.2019.08.018
65. Shen K, Li R, Zhang X, et al. Acetyl oxygen benzoate engeletin ester promotes KLF4 degradation leading to the attenuation of pulmonary fibrosis via inhibiting TGFβ1-smad/p38MAPK-lnc865/lnc556-miR-29b-2-5p-STAT3 signal pathway. *Aging*. 2021;13(10):13807–13821
66. Liu P, Zhao L, Gu Y, Zhang M, Gao H, Meng Y. LncRNA SNHG16 promotes pulmonary fibrosis by targeting miR-455-3p to regulate the Notch2 pathway. *Respir Res*. 2021;22(1):44. doi:10.1186/s12931-021-01632-z

67. Yang L, Liu X, Zhang N, Chen L, Xu J, Tang W. Investigation of circular RNAs and related genes in pulmonary fibrosis based on bioinformatics analysis. *J Cell Biochem*. 2019;120(7):11022–11032. doi:10.1002/jcb.28380
68. Li J, Li P, Zhang G, Qin P, Zhang D, Zhao W. CircRNA TADA2A relieves idiopathic pulmonary fibrosis by inhibiting proliferation and activation of fibroblasts. *Cell Death Dis*. 2020;11(7):553. doi:10.1038/s41419-020-02747-9
69. Yao W, Li Y, Han L, et al. The CDR1as/miR-7/TGFBR2 axis modulates EMT in silica-induced pulmonary fibrosis. *Toxicol Sci*. 2018;166 (2):465–478. doi:10.1093/toxsci/kfy221
70. Zhang L, Chi X, Luo W, et al. Lung myofibroblast transition and fibrosis is regulated by circ0044226. *Int J Biochem Biotechnol*. 2020;118:105660. doi:10.1016/j.biocel.2019.105660
71. Xu Q, Cheng D, Li G, et al. CircHIPK3 regulates pulmonary fibrosis by facilitating glycolysis in miR-30a-3p/FOXK2-dependent manner. *Int J Bio Sci*. 2021;17(9):2294–2307. doi:10.7150/ijbs.57915
72. Zhang JX, Lu J, Xie H, et al. CircHIPK3 regulates lung fibroblast-to-myofibroblast transition by functioning as a competing endogenous RNA. *Cell Death Dis*. 2019;10(3):182. doi:10.1038/s41419-019-1430-7
73. Bai J, Deng J, Han Z, et al. CircRNA_0026344 via exosomal miR-21 regulation of Smad7 is involved in aberrant cross-talk of epithelium-fibroblasts during cigarette smoke-induced pulmonary fibrosis. *Toxicol Lett*. 2021;347:58–66. doi:10.1016/j.toxlet.2021.04.017