REVIEW

MicroRNAs in idiopathic pulmonary fibrosis: involvement in pathogenesis and potential use in diagnosis and therapeutics

Huimin Li, Xiaoguang Zhao, Hongli Shan, Haihai Liang*

Department of Pharmacology, College of Pharmacy, Harbin Medical University, Harbin 150081, China

Abstract MicroRNAs (miRNAs) are a class of phylogenetically conserved, non-coding short RNAs, 19–22 nt in length which suppress protein expression through base-pairing with the 3′-untranslated region of target mRNAs. miRNAs have been found to participate in cell proliferation, differentiation and apoptosis. Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, and high lethality fibrotic lung disease for which currently there is no effective treatment. Some miRNAs have been reported to be involved in the pathogenesis of pulmonary fibrosis. In this review, we discuss the role of miRNAs in the pathogenesis, diagnosis and treatment of IPF.

*Corresponding author.
   E-mail address: lianghaihai@ems.hrbmu.edu.cn (Haihai Liang).

1. Introduction

Idiopathic pulmonary fibrosis (IPF) is an interstitial lung disease with unknown cause and unclear pathogenesis. Of the idiopathic interstitial pneumonia family of diseases, it is the most common and has the highest morbidity and worst prognosis. Currently, there is no effective treatment for IPF[1].

The formation of fibroblastic foci and the excessive deposition of extracellular matrix (ECM) are regarded as factors that directly induce IPF[2]. Myofibroblasts, which have the features of both fibroblasts and smooth muscle cells, overexpress α-smooth muscle actin (α-SMA) and extensively synthesize and secrete ECM. Finally, they lead to the remodeling of lung tissue observed in IPF patients[3–5]. Previous research has shown that myofibroblasts in the lung arise mainly from fibroblasts and epithelial cells and, to a lesser extent, from circulating fibroblasts derived from bone marrow cells. Of these, fibroblasts and epithelial cells are considered to be the main sources of myofibroblasts[6–8].

MicroRNAs (miRNAs) are a class of non-coding single-stranded RNAs, 19–22 nt in length, which can complementary base-pair to the 3′-untranslated region (UTR) of targets and repress the translation of target genes or degradation of target mRNAs[9]. Recently, as the result of an in-depth study of miRNAs, we found that deregulation of miRNAs participates in the progression of fibrosis in different tissues including liver, kidney and myocardium. Here, we review the key roles played by miRNAs in the pathogenesis of IPF and their significance in its diagnosis and treatment (Fig. 1 and Table 1[10–40]).

2. The role of miRNAs in alveolar epithelial cells of IPF

Normal epithelial cells are closely linked to each other through the intercellular adhesion mechanism. E-cadherin is a key component in the tight junctions of epithelial cells where it maintains their integrity and polarity. The ability of epithelial cells to change into mesenchymal cells through the epithelial–mesenchymal transition (EMT) plays an important role in the development of IPF. As a result of the EMT, alveolar epithelial cells (AECs) lose their intrinsic polarity and intercellular adhesion and gain the ability to migrate. AECs produce a large amount of ECM which eventually leads to the development of fibrosis[7]. Current studies confirm that many miRNAs including let-7d, miR-200, miR-26a and miR-375 participate in IPF through regulating EMT[19,23–26,29,40–42]. They also have reduced expression in IPF patients whereas the expression of their target gene, high-mobility group A protein 2 (*HMGA2*), is obviously up-regulated. This leads to a change in epithelial cell phenotype, the deposition of collagen and development of IPF.

Table 1 Role of microRNAs in idiopathic pulmonary fibrosis.

Putative role	No.	miRNA	Target	Tissue/Cell type	Ref.
Pro-fibrotic	1	miR-21	Smad7	Mice/MRC-5	10,11
	2	miR-199a-5p	CAV-1	Mice/MRC-5	12
	3	miR-145	KLF4	Mice/MRC-5	13
	4	miR-154	CDKN2B	NHLF	14
	5	miR-155	KGF	NHLF	15
	6	miR-96	FoxO3	NHLF	16
	7	miR-142-5p	SOCS1	Mice/ Macrophages	17
	8	miR-210	MNT	NHLF	18
				IPF fibroblasts	
Anti-fibrotic	9	Let-7d	HMGA2	Mice/A549,FLF, NHLF, HFF-1	19,20
	10	miR-26a	CTGF/Smad4/CCND2	Mice/MRC-5	21
			HMGA2	NHLF	22
				Mice/A549	23
	11	miR-375	Frizzled 8	Rat/AEC II	24
	12	miR-200		Mice/	25
				AEC, RLE-6TN	
	13	miR-1343	TGFBR1/TGFBR2	A549	26
	14	miR-31	RhoA, Integrin α_5	Mice/MRC-5	27
				IPF fibroblasts	
	15	miR-27a-3p	α-SMA, Smad2, Smad4	IPF fibroblasts	28
	16	miR-27b	Gremin1	A549	29
	17	miR-92a	WISP1	Mice/ NHLF	30
	18	miR-486-5p	Smad2	Mice/NIH/3T3	31
	19	miR-9-5p	TGFBR2, Nox4	Mice/ NHLF	32
	20	miR-153	TGFBR2	MRC-5	33
	21	miR-29	ITGA11, ADAMTS9,	Mice	34,35
			ADAM12, NID1	Mice/IMR-90	36
				IMR-90	37
				IPF fibroblasts	38
	22	miR-17~92	DNMT1	NHLF	39
				IPF fibroblasts	
	23	miR-130a-3p	PPARγ	Mice/Macrophages	17
	24	miR-326	TGF-β1	Mice/A549, NIH/3T3	40

NHLF, normal human lung fibroblast; FLF, human fetal lung fibroblast; HFF-1, human fetal foreskin fibroblasts.
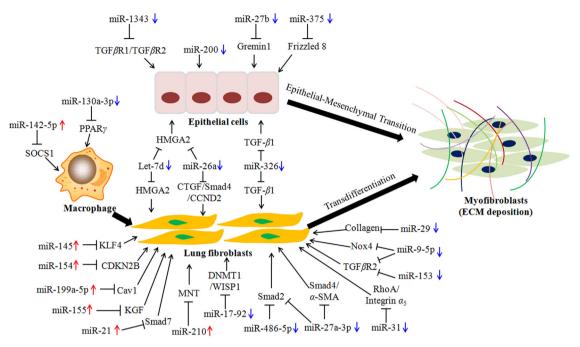
Figure 1 The alteration of miRNAs and their role in the progression of IPF.

Let-7 was originally discovered in *Caenorhabditis elegans* where its role is to regulate cell differentiation and proliferation, a role conserved in different species. The human let-7 family includes 12 members (let-7a1, -a2, -a3, -b, -c, -d, -e, -f1, -f2, -g, -i and miR-98), located on 8 different homologous chromosomes[43]. Through miRNA microarray analysis of lung tissue from healthy controls and IPF patients, Pandit et al.[19] found that levels of 18 miRNAs including let-7d were reduced in IPF patients. They also found that the expression of let-7d was decreased and the expression of HMGA2 was increased in A549 AECs stimulated by TGF-β1. This was subsequently shown by electrophoretic mobility shift assays, chromatin immunoprecipitation and luciferase assays, resulting from binding between Smad3 and the let-7d promoter. In addition, specific inhibition of let-7d in mouse lung tissue was shown to induce the EMT thereby increasing the thickness of the alveolar walls and eventually causing pulmonary fibrosis.

It has been reported that miR-26a plays an important role in the regulation of many diseases. Harada et al.[44] confirmed that miR-26a can inhibit cardiac fibroblast proliferation and differentiation by down-regulating the expression of TRPC3 and thereby control atrial fibrillation. Wei et al.[45] showed that miR-26a decreased the expression of collagen I which is induced by angiotensin II (Ang-II) and up-regulated the expression of connective tissue growth factor (CTGF). All these results indicate that miR-26a has the ability to prevent fibrosis.

In our study, differential expression and cluster analysis using a bioinformatics method showed that genes participating in EMT were differentially expressed in lung tissue of IPF patients, a result validated by immunofluorescence in pulmonary fibrotic mice. Moreover, we confirmed that miR-26a regulated EMT by binding to the *HMGA2* gene and inhibiting its expression. Moreover, forced expression of miR-26a inhibited the occurrence of EMT and the expression of EMT-related genes. Taken together, our study confirms that miR-26a inhibits EMT and thereby reduces the occurrence of IPF[23].

The TGF-β and Wnt pathways are the most well-known pathways involved in lung fibrosis. Besides participating in the proliferation and differentiation of fibroblasts, they also promote EMT. A recent study by Das et al.[40] showed that miR-326 was reduced in lung fibrosis causing induction of TGF-β1. In contrast, enhanced expression of miR-326 dampens lung fibrosis by post-transcriptional regulation of TGF-β1. Alternatively, Stolzenburg et al.[26] found that miR-1343 attenuates EMT and fibrogenesis by directly targeting TGF-β receptors 1 and 2. In another study, Wang et al.[24] found that miR-375 was decreased during trans-differentiation of AECs and that ectopic expression of miR-375 inhibited EMT by direct binding to the 3′-UTR of Frizzled 8 and thereby blocked the Wnt/β-catenin pathway.

Previous studies have shown that the expression of the miR-30 family (miR-30a, miR-30c, miR-30d and miR-30e) is down-regulated in patients with IPF[19]. miR-30c and miR-30e are located in the intron of nuclear transcription factor Y subunit γ (NFYC) and can inhibit the expression of Smad3. In the lung tissue of IPF patients, the level of NFYC mRNA is significantly reduced. Studies found that miR-30 was located in AECs and that down-regulation of miR-30 increased the expression of endothelin receptor A and HMGA2 leading to EMT and the deposition of collagen[41]. In addition, the miR-200 family, whose over-expression can inhibit the EMT, was down-regulated in IPF patients. Injection of miR-200 to mice clearly enables them to resist pulmonary fibrosis[25].

3. The role of miRNAs in fibroblasts of IPF

Proliferation of fibroblasts and their differentiation into myofibro-blasts are important in the development of IPF. Several studies have shown that some miRNAs including miR-21, miR-155, miR-26a, miR-27a-3p and miR-9-5p can regulate the function of fibroblasts in lung[12–16,18,20,21,27,28,30–33,41,46].

The *miR-21* host gene in human is located on chromosome 17p23 and has independent promoters for transcription. miR-21 is widely expressed in tissues and is not essential for normal tissue development as verified by knockout of *miR-21* in mice[47]. Liu

et al.[10] found that miR-21 is up-regulated in IPF patients and only a small amount of miR-21 is expressed in normal lung tissue of mice. However, after stimulating with bleomycin, the expression of miR-21 was clearly up-regulated which promoted the accumulation of myofibroblasts. The research showed that even at 5–7 days after the lung injury, the expression of miR-21 could be inhibited by an miR-21 antisense probe sufficiently to reduce or eliminate IPF. TGF-β1 is the most important pro-fibrogenic cytokine which increases the expression of miR-21 in lung fibroblasts. Further studies showed that *Smad7* is a direct target gene of miR-21. Thus, miR-21 causes the activation of the TGF-β1 pathway and ultimately promotes the occurrence and development of IPF by targeting *Smad7*. Taken together, TGF-β1 promotes IPF by regulating an miR-21/Smad7 feedback loop[11,48].

Our research has revealed that the expression of miR-26a is significantly reduced in lung tissues of mice and patients with IPF accompanied by activation of the TGF-β1 pathway and increased expression of the miR-26a target protein CTGF. Inhibition of miR-26a promotes collagen deposition in the lungs of mice. In contrast, over-expression of miR-26a inhibits experimental pulmonary fibrosis in mice. Further studies confirmed that miR-26 inhibits lung fibrosis through its ability to regulate the expression of CTGF and thereby inhibit the differentiation and proliferation of fibroblasts.

We also found that *Smad3*, a downstream gene of TGF-β1, inhibits the expression of miR-26a and that miR-26a affects the nuclear translocation of Smad3 by regulating Smad4. The TGF-β1 pathway is activated by external stimulation to phosphorylate Smad3 which translocates into the nucleus and inhibits the expression of miR-26a. Subsequently post-transcriptional expression of CTGF promotes the differentiation and proliferation of fibroblasts in lung and further increases the collagen content. In addition, down-regulation of miR-26a increases the expression of Smad4 and promotes the translocation of Smad3 to the nucleus to inhibit the expression of miR-26a. This loop repeats and aggravates pulmonary fibrosis. Furthermore, treatment with exogenous miR-26a leads to inhibition of Smad3 translocation such that Smad3 inhibition of miR-26a vanishes, further strengthening the therapeutic effect of miR-26a. The above results indicate that miR-26a inhibits the proliferation and differentiation of fibroblasts by targeting CTGF and then reduces collagen secretion to ultimately reduce pulmonary fibrosis. Further evidence of the potential of miR-26a to prevent and treat pulmonary fibrosis[21] comes from Li et al.[22] who confirmed that it regulates cyclin D2 (*CCND2*) and inhibits the proliferation of fibroblasts induced by activation of TGF-β1.

The *miR-155* gene located on chromosome 21p21 generates miR-155 in hematopoietic cells to play an important role in inflammatory and immunological reactions[49]. Marshall et al.[50] found that it participates in pulmonary fibrosis by targeting the Ang-II type 1 receptor (AT1R) which is located in stromal fibroblasts and has increased expression in lungs of IPF patients and in mice treated with bleomycin. This increased expression enhances collagen synthesis in fibroblasts and promotes the development of pulmonary fibrosis. Furthermore, Pottier et al.[15] showed that miR-155 is up-regulated in fibrotic mice. Functional studies have demonstrated that the keratinocyte growth factor gene (*KGF*) is a direct target of miR-155, up-regulation of which inhibits *KGF* expression. After transfection of miR-155, the migration ability of fibroblasts was significantly increased[15].

miR-31 is a negative regulator of pulmonary fibrosis. It is found that miR-31 expression is reduced in the lungs of mice with experimental pulmonary fibrosis and in IPF fibroblasts. Over-expression of miR-31 inhibits fibrogenic, contractile and migratory activities of fibroblasts *in vivo* to alleviate bleomycin-induced pulmonary fibrosis[27].

An increasing number of studies[51–53] have shown that the generation of reactive oxygen species (ROS) contributes to the pathogenesis of fibrotic diseases including IPF. A recent study showed that hydrogen peroxide (H_2O_2) cause the dysregulation of many miRNAs in human fetal lung fibroblasts (HFL-1)[32]. Among them, miR-9-5p was identified as being anti-fibrotic because of its reduced response to H_2O_2, and because many genes involved in the TGF-β pathway are its predicted targets. Another study showed that miR-9-5p was down-regulated in a mouse model of lung fibrosis and in IPF patients. Moreover, forced expression of miR-9-5p attenuated the TGF-β1-induced fibrogenic pathway in HFL and prevented experimental lung fibrosis in mice by regulating expression of TGF-β receptor type II (TGFBR2) and NADPH oxidase 4 (NOX4)[32].

4.   miRNAs inhibit collagen deposition and regulate the synthesis of ECM in IPF

IPF is induced by the necrosis of parenchymal cells that result from inflammation and deposition of ECM. If the synthesis of ECM and collagen deposition are inhibited, the development of IPF can be greatly weakened or even eliminated. Current studies confirm that miRNAs can participate in pulmonary fibrosis by directly regulating the generation of collagen[34,36,41,54–56].

Cushing et al.[51] found that the expression of miR-29 was significantly reduced in mice with bleomycin-induced pulmonary fibrosis and down-regulated in human embryonic lung fibroblasts (IMR-90) stimulated by TGF-β1. This suggests that miR-29 may be involved in pulmonary fibrosis. A further study showed that down-regulation of miR-29 was negatively related to the up-regulation of genes, promoting fibrosis such as the collagen genes in ECM and basement membrane[57]. In fact many genes which regulate ECM, such as *ELN*, *FBN1*, *COL1A1*, *COL1A2* and *COL3A1*, are target genes of miR-29[57]. In addition, miR-29 inhibits TGF-β1-induced ECM synthesis in human lung fibroblasts through activating the PI3K/AKT pathway[37]. Furthermore, studies have shown[34,35,55] that over-expression of miR-29 can inhibit bleomycin-induced pulmonary fibrosis in mice. More importantly, a recent study by Khalil et al.[38] showed that interaction of IPF fibroblasts with collagen 1 resulted in decreased protein phosphatase (PP) 2A and histone deacetylase (HDA) C4 phosphorylation leading to decreased nuclear translocation of HDAC4 and finally reduction of miR-29 and a pathological increase in type I collagen expression.

The TargetScan database (http://www.targetscan.org/) predicts that *Col1a2* (Collagen, type 1, α2) is a potential target of miR-26a. Wei et al.[45] confirmed that miR-26a directly regulates *Col1a2* and inhibits cardiac fibrosis. The issues of whether *Col1a2* also mediates the anti-fibrotic effects of miR-26a and whether there are other miRNAs directly regulating collagen synthesis in pulmonary fibrosis warrant further research.

5.   miRNAs participate in pulmonary fibrosis through other mechanisms

miRNAs participate in IPF by multiple mechanisms. Methylation, including DNA methylation and histone methylation, is one of the

important ways that genes are regulated which is closely related to embryonic development, aging, cancer and many other physiological and pathological processes[58–60]. Some recent studies suggest that deregulation of methylation may be involved in the fibrotic process[61–63]. For example, in IPF patients, 80% of the miR-17~92 cluster promoter was found to be occupied by areas of cytosine polyguanine (CPG) and was significantly hyper-methylated compared with normal lung tissue. A further study showed that introduction of miR-17~92 into lung fibroblasts of IPF patients reduced the expression of many fibrotic genes such as *CTGF*, *COL1A1* and *COL13A1* by direct regulation of DNA methyltransferase-1 (DNMT-1)[39].

On this basis, we hypothesize that miRNAs are involved in IPF through complex pathways. For instance, miRNAs can participate in pulmonary fibrosis by regulating early inflammation of lung damage indicating they may be therapeutic targets in IPF[17,64]. Zhang et al.[64] found that miR-199a-5p was increased in cystic fibrosis (CF) macrophages and lung tissue which induced a hyper-inflammatory response in CF MΦs through targeting caveolin-1 (CAV1) to activate toll-like receptor 4 (TLR4) signaling. Further-more, inhibition of miR-199a-5p restored CAV1 expression and alleviated the hyper-inflammation in CF MΦs. In addition, Su et al.[17] confirmed that miR-142-5p and miR-130a-3p regulate macrophage fibrogenesis in liver fibrosis and lung fibrosis. They found that the up-regulation of miR-142-5p and down-regulation of miR-130a-3p in macrophages in response to interleukin (IL)-3 in tissue samples from patients with liver cirrhosis and IPF by direct regulation of their targets, the suppressor of cytokine signaling 1 (*SOCS1*) and peroxisome proliferator-activated recep-tor γ (*PPARγ*), respectively. More importantly, inhibition of miR-142-5p or over-expression of miR-130a-3p attenuated liver fibrosis and lung fibrosis in mice.

6. Deregulated miRNA network in IPF

It is known that one miRNA can regulate several target genes and one gene can be regulated by several miRNAs at the same time. In addition, many fibrosis related genes such as *TGF-β1* and *HIF-1* can act as transcription factors to regulate the expression of miRNAs. Thus, miRNAs and their targets form a complex network in the process of IPF.

Smad3, a transcription factor, can regulate the expression of many miRNAs including let-7d and miR-154. Using electrophore-tic mobility shift assays, chromatin immunoprecipitation and luciferase assays, Pandit et al.[19] confirmed that TGF-β1 inhibits the expression of let-7d by promoting Smad3 to bind with its promoter. Milosevic et al.[14] found that Smad3 binds to the 322 bp site of the miR-154 precursor and regulates its expression. Our group found that p-Smad3 influenced the down-regulation of miR-26a and that, moreover, miR-26a inhibited the nuclear transcription of p-Smad3 by regulating Smad4[21]. One can speculate that miR-26a affects the generation of other miRNAs by regulating Smad3 and that miRNAs interact with each other and exert synergistic roles in pulmonary fibrosis.

Some studies have shown that miRNAs can regulate the generation of other miRNAs. Chen et al.[65] found that miR-107, by binding to the let-7 sequence, inhibited the expression of let-7 and induced the initiation and metastasis of breast cancer. Guo et al.[66] constructed an miRNA–miRNA interaction network involving a mutual regulatory pattern in different species. In recent work in our laboratory, we showed that miR-26a increased

the expression of let-7d by regulating Lin28B suggesting that miR-26a and let-7d act synergistically to ameliorate pulmonary fibrosis[42]. Furthermore, miR-26a reduces the expression of miR-21 possibly through the mediation of Smad3 or another transcription factor. Based on these results, we constructed an miRNAs-transcription factor (TF)-miRNAs regulation network in IPF which warrants further validation through future experiments.

We also analyzed the miRNA expression profile in IPF using the microarray dataset (GSE32538)[67]. Surprisingly, we found that more than 80% of miRNAs were down-regulated in IPF patients. This is consistent with the results of previous studies showing miRNAs are decreased in the lungs of mice with experimental pulmonary fibrosis and in IPF and that they all exert potential anti-fibrotic effects in the progression of IPF (Table 1). Thus, further studies are needed to investigate what causes the global down-regulation of miRNAs in IPF.

7. miRNAs act as biomarkers for early diagnosis of IPF

miRNAs that are differentially expressed in respiratory diseases may be biomarkers for their diagnosis, molecular classification and prognosis. The existing literature indicates that (1) miR-21 and miR-126 are up-regulated and miR-672 and miR-143 are down-regulated in an asthmatic rat model[68] and (2) miR-155, miR-21, miR-17-92 and miR-221/222 are up-regulated and let-7, miR-1, miR-29 and miR-126 down-regulated in lung cancer[69]. In fact, studies[70,71] have shown that different sub-types of lung cancer or non-cancer diseases can be distin-guished by their miRNA expression profiles. For example, Chen et al.[70] reported that eight miRNAs are differentially expressed in the serum of lung cancer patients compared with normal lung tissues.

Lam et al.[71] showed that the expression of miR-26a was significantly decreased in rats with experimental silicosis and patients with lung cancer. Furthermore, miR-26a was significantly down-regulated in lung tissues and sputum of rats exposed to cigarette smoke[72,73]. van Pottelberge et al.[72] reported that miR-26a was clearly down-regulated in the plasma of patients with chronic obstructive pulmonary disease (COPD) compared with normal smokers. However, a study by Ezzie et al.[74] found no obvious differential expression of miR-26a in COPD patients compared to normal controls. Therefore, there is still debate about the role of miR-26a in COPD.

Yang et al.[75] found 47 differentially expressed miRNAs in the serum of IPF patients including 21 that were up-regulated and 26 down-regulated. The results of quantitative RT-PCR confirmed that expression of miR-21, miR-199a-5p, and miR-200c was significantly increased in serum of IPF patients while the opposite was true for miR-31, let-7a and let-7d. These results suggest that miRNAs may be useful diagnostic markers for the diagnosis, prognosis and treatment of IPF[76].

8. miRNAs as therapeutic targets in IPF

The fact that abnormal expression or mutation of miRNAs leads to disease suggests specific miRNAs can be used as potential targets for their treatment and control. Theoretically, the expression of down-regulated miRNAs in IPF can be restored by importing an adenovirus vector that contains the target miRNA. Conversely, up-regulated miRNAs can be down-regulated using an antisense oligonucleotide such as 2′-O-methyl, 2′-O-methoxy ethyl and

locked nucleic acid (LNA) antisense oligonucleotides to directly bind to miRNAs and block their activity[77].

Lanford et al.[78] found that treatment of chronically infected chimpanzees with an LNA-modified oligonucleotide (SPC3649) complementary to miR-122 suppressed hepatitis C virus (HCV) viremia with no evidence of viral resistance or side effects. Phase I research on SPC3649 has now been completed and a phase IIA clinical trial begun. SPC3649 may be the first drug that targets miRNAs to be used in the treatment of a human disease.

In a mouse model of myocardial hypertrophy, inhibiting miR-21 with an antagonist was found to decrease the activity of ERK/MAPK, block the myocardial interstitial fibrosis and reduce myocardial dysfunction[79]. Similarly, in renal fibrotic mice, inhibiting the expression of miR-21 reduced renal damage[80]. Meng et al.[81] were the first to report that chemotherapeutic drugs can affect miRNA expression in human cancer cells. They found that treating tumor cell xenografts with systemic gemcitabine altered the expression of miRNAs. They also found that miR-21 was up-regulated in bile duct cancer cells which increased their sensitivity to chemotherapeutic drugs[81]. Kota et al.[82] successfully delivered miR-26a to mice with liver cancer using an adeno-associated virus (AAV) and found that AVV did not integrate into the human genome although it was clearly present in liver cells. These findings may provide new hope for the treatment of liver cancer.

Although extensive research has revealed the mechanisms of miRNAs in IPF and shown their therapeutic potential, clinical application of miRNAs is confronted with many problems. One is the lack of targeted miRNA delivery technology to solve off-target effects and improve the safety of miRNAs *in vivo*.

9. Long non-coding RNAs (lncRNAs) in pulmonary fibrosis

Long non-coding RNAs (lncRNAs) are a class of non-coding RNAs with more than 200 nucleotides (nt) without protein-coding function[83]. There is a great deal of evidence showing that they play a major role in various diseases, including cancer, cardiovascular disease and lung disorders[84,85]. Recently, lncRNAs have been recognized as pivotal mediators in the initiation and maintenance of various cancers and heart diseases by competitive binding miRNAs[86–88]. However, the role and mechanisms of lncRNAs in pulmonary fibrosis remains largely elusive.

Cao and colleagues[89] firstly identified the differential expression profile of lncRNAs in bleomycin-induced lung fibrosis in mice. Of the many lncRNAs, 210 were up-regulated and 358 down-regulated. In this study, they also validated two up-regulated lncRNAs, AJ005396 and S69206, in fibrotic lung tissue by *in-situ* hybridization[89], In addition, Sun et al.[90] identified the differential expression of lncRNAs in paraquat-driven experimental lung fibrosis in mice, and also found that forced expression of the lncRNAs, uc.77 and 2700086A05Rik, caused EMT by regulation of *Zeb2* and *Hoxa3* and contributed to lung fibrosis.

Song et al.[91] identified two other up-regulated lncRNAs, MRAK088388 and MRAK081523, in lung fibrosis and found that MRAK088388 regulates *N4bp2* by sponging miR-29b-3p whereas MRAK081523 regulates *Plxna4* by binding to let-7i-5p. This indicates that MRAK088388 and MRAK081523 display regulatory functions as competing endogenous RNAs (ceRNAs) and contribute to pulmonary fibrosis. In addition, a recent study by Huang et al.[92] found 34 lncRNAs containing potential binding sites for several well-known lung fibrosis-related miRNAs including miR-21, miR-31, miR-101, miR-29, miR-199 and let-7d. They

then tested and confirmed four lncRNAs which were inversely correlated to the miRNA expression in IPF. Further study revealed that silencing the lncRNA CD99 molecule pseudogene 1 (CD99P1) inhibited fibrogenesis in lung fibroblasts whereas knockdown of lncRNA n341773 promoted it[92].

At the present time, detailed insight into the regulation and biological roles of lncRNAs in lung fibrosis is just beginning to emerge. A more detailed and integrated understanding of their action and mechanisms in pulmonary fibrosis could help pave the way for effective treatment options for fibrotic-related lung disease.

10. Conclusions and perspectives

Targeting specific miRNA has great potential in the treatment of pulmonary fibrosis. In theory, molecular target therapy has highly specific effects on target cells and can efficiently reduce damage to normal tissue. However, there are many problems to solve before miRNA pharmacotherapy of IPF can be introduced. These include: (1) How do we accurately confirm the target miRNA and its target gene experimentally and in clinical practice and accurately control the targeting of miRNAs; (2) Are the *in vivo* metabolic pathways of nucleic acid drugs clearly known on the basis of the relevant pharmacokinetic knowledge; (3) Is it feasible to interfere with miRNAs in the human body and will such interference bring unexpected adverse reactions; (4) How are miRNAs or antisense nucleotide inhibitors introduced into target cells safely and effectively; and (5) If we develop effective treatments based on interfering with miRNAs, will the cost be too high.

Although treatment of IPF with miRNAs may have defects, miRNAs probably represent the most exciting intervention target of the last ten years. In the future, we have reason to hope miRNAs or their inhibitors will form the basis of an effective treatment to alleviate the suffering of IPF patients.

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