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Non-coding RNA in idiopathic interstitial pneumonia and Covid-19 pulmonary fibrosis

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Abstract

Pulmonary fibrosis is the key feature of majority of idiopathic interstitial pneumonias (IIPs) as well as many patients with post-COVID-19. The pathogenesis of pulmonary fibrosis is a complex molecular process that involves myriad of cells, proteins, genes, and regulatory elements. The non-coding RNA mainly miRNA, circRNA, and lncRNA are among the key regulators of many protein coding genes and pathways that are involved in pulmonary fibrosis. Identification and molecular mechanisms, by which these non-coding RNA molecules work, are crucial to understand the molecular basis of the disease. Additionally, elucidation of molecular mechanism could also help in deciphering a potential diagnostic/ prognostic marker as well as therapeutic targets for IIPs and post-COVID-19 pulmonary fibrosis. In this review, we have provided the latest findings and discussed the role of these regulatory elements in the pathogenesis of pulmonary fibrosis associated with Idiopathic Interstitial Pneumonia and Covid-19.

Keywords Pulmonary fibrosis · IIP · Covid-19 · lncRNA · miRNA · circRNA

Introduction

There are myriads of conditions such as auto-immune diseases, exposure (drugs or environmental antigens), and infections which can cause pulmonary fibrosis. However, in a large group of patients, the cause remains unknown and the condition is classified as idiopathic interstitial pneumonia (IIP) [1]. Idiopathic Pulmonary Fibrosis (IPF) and Non-Specific Interstitial Pneumonia (NSIP) are classical examples of IIP. Pulmonary fibrosis, whether caused by IPF or NSIP, is relentlessly progressive, posing a threat of respiratory failure and even death. It is unfortunate that the

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current therapeutic options can only marginally slow down the progression of pulmonary fibrosis in IIPs, but cannot reverse the condition. Recently, Covid-19 has also led to the addition of a large number of patients with post-infectious lung changes. Despite the fact that the changes are largely reversible, pulmonary fibrosis has risen dramatically in the aftermath of Covid-19 as a sequela and the treatment for the same is largely unknown [2] [3].

Pulmonary fibrosis occurs as a result of interplay of multiple complex processes that include lung injury, abnormal tissue repair, fibro-proliferation, and extracellular matrix deposition [4]. Various pathways involved in the pathogenesis of pulmonary fibrosis include apoptosis, inflammation, coagulation, angiogenesis, and proteolytic/anti-proteolytic balance [5]. Many of these processes and pathways are regulated by the changes in the expression of various protein-coding genes which play vital role in the pathogenesis of pulmonary fibrosis. Many of these genes are further regulated by different classes of non-coding RNAs. It has been reported that genetic and epigenetic defects in miRNA and other ncRNAs and their processing machinery are common trademarks of many cancers in humans [6]. These ncRNAs can also contribute to the progression of multiple other human disorders [6]. Recent studies have demonstrated the role of non-coding RNAs in various pulmonary diseases and their critical roles in lung development and homeostasis that offers a new paradigm for pulmonary disease diagnosis, control, and treatment [7]. The current article provides a comprehensive review of the role of ncRNAs in pulmonary fibrosis associated with IIPs and Covid-19/post-Covid pulmonary fibrosis.

Non-coding RNAs

Non-coding RNAs (ncRNA) are transcripts that do not code for any protein, nevertheless, it does not mean that these entities are non-functional. These ncRNAs control diverse levels of gene expression in various biological processes including transcription, chromatin remodeling, RNA editing, splicing as well as translation and turnover [8]. There are mainly three kinds of non-coding RNAs that are functionally important: long non-coding RNAs (lncRNAs), circular RNAs (cirRNAs), and microRNAs.

Classification of ncRNAs

In general, ncRNAs can be classified based on length, with short or small non-coding RNAs having a length of below 200 nucleotides (except for SnoRNA whose length can vary between 60 bps to 300bps)[9]. Another way of classification is based on functionality such as housekeeping ncRNAs

that includes ribosomal RNAs (rRNAs) and transfer RNA (tRNA), or regulatory ncRNAs such as micro RNAs (miR-NAs), small nuclear RNAs (snRNAs), piwi-interacting RNAs (piRNAs), tRNA derived small RNAs (tsRNAs) and long noncoding RNAs (lncRNAs) [10]. There is another class of ncRNAs called circular RNAs, consisting of a covalently closed continuous loop lacking both 5' cap and 3' tail [11]; it is also regulatory in nature. Figure 1 summarizes the three main non-coding RNA and their biogenesis. Below we have discussed all three key ncRNAs.

Micro RNAs, ~ 22 nucleotides long and single stranded ncRNAs, are expressed endogenously and regulate the gene expression at post transcriptional level. Genes that encode miRNAs are ubiquitously present in the genome. Partly, miRNAs are encoded inside or overlap with protein-coding or non-coding genes that relate their expression to the transcription and processing of such genes present in the host. Additionally, miRNA can also originate from autonomous transcription units [12]. During the biogenesis of the miRNA, it passes through multiple processes such as transcription, nuclear maturation, exportation followed by cytoplasmic processing before evolving into a functional entity [10].

LncRNAs are defined as the transcripts longer than 200 nucleotides. LncRNAs comprise the major portion of the ncRNA, however, as compared to miRNA they are not well studied [10]. During the last decade, as a result of advancements in the high-throughput sequencing and computational analysis, lncRNA has become a hotspot in scientific research. lncRNA biogenesis takes place in the nucleus and is expressed in a tissue specific manner [13]. It mimics the mRNA synthesis process, the promoter of lncRNA is often marked with epigenetic markers which are transcribed by Pol II or Pol III and post-transcriptional modification which is characterized by 5' capping and 3' polyadenylation [10].

Circular RNA (CircRNAs) are non-coding transcripts that originate due to the back-splicing mechanism which results in joined head-to-tail splice sites followed by circularization of introns or exons [14]forming covalently linked circular RNA molecules [14]. The size of circRNA can vary from 100 nucleotides to over 4 kb and can harbour single or multiple exons [15], [16]. They are highly stable due to lack of ends and are highly tissue/cell-specific in nature [14] [8].[14].

Pulmonary fibrosis and non-coding RNA

In the last decade, there has been a rapid increase in studies exploring the role of non-coding RNA in pulmonary fibrosis. IPF is one of the commonest IIPs and also the most widely studied pulmonary fibrosis phenotype. However,
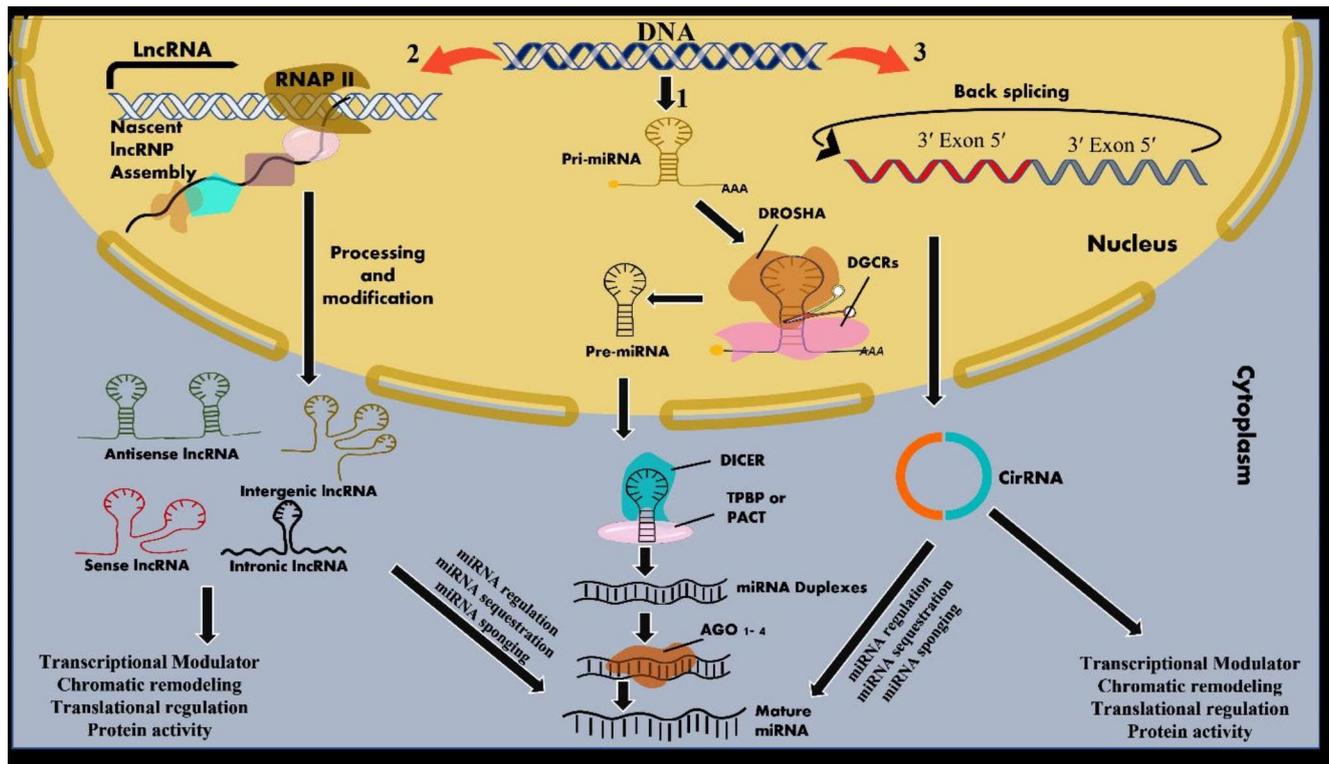
Fig. 1 Biogenesis and Major functions of ncRNAs

even after decades of efforts on the pathogenesis of the IPF, the exact etiology of pulmonary fibrosis for this disease is still not well-defined. Recent data suggest that intricate network of coding and non-coding RNAs (mRNA/LncRNA/miRNA/CircRNA) play crucial role in the pathogenesis of pulmonary fibrosis [18].

In the following sections, we have discussed the role of these ncRNA in pulmonary fibrosis associated with IIPs and Covid-19.

miRNA

Among ncRNAs, the miRNA is the most widely studied for pulmonary fibrosis in animal models, cell lines, as well as in human samples. One of the initial studies by Caedens et al., reported the overexpression of miR-199a-5p in the lungs of IPF patients and bleomycin induced mouse models. The study demonstrated that miR-199a-5p activates the fibroblasts by targeting CAV-1 and modulation of TGF-β signaling [19]. Likewise, miR-133a inhibits the differentiation of myofibroblast by targeting and reducing the expression of TGF-β receptor 1, CTGF, and collagen type 1-a1; thus, ameliorating pulmonary fibrosis [20]. Pandit et al., showed that out of 450 miRNAs, around 10% of the miRNAs are dysregulated in IPF patients [21]. In their work, they have demonstrated decreased expression of let-7d in IPF patients, while inhibition of let-7d in mice model led to the increase

in the expression of α-SMA, N-cadherin-2, vimentin, and HMGA2, confirming profibrotic effects.

Liu et al., demonstrated that miR-21 was upregulated in the peripheral blood of IPF patients. Inhibition of this target in animal model upregulates the ADAMTS-1, which eventually downregulates the Col1 and Col3 collagen and reduces the IPF progression [22]. miR-21 is also involved in lung injury and fibrosis; as shown in animal models, knocking out of this miRNA ameliorates the lung injury and inflammation [23]. miR-22 is another miRNA playing important role in pulmonary fibrosis, as observed in BLM-induced mice. In-vitro experiments suggest that miR-22 transfection suppresses TGF-β1-induced expression of α-SMA via ERK1/2 pathway inhibition. In presence of TGF-β1, miR-22 negatively regulates the connective tissue growth factor [24].

miRNA also regulates the fibrogenic effects of macrophages. In macrophages of IPF patients and BLM induced mice, the overexpression of miR-142-5p and downregulation of miR-130a-3p have been observed which is induced by IL-3 and IL-4. The overexpression of miR-142-5p and reduced expression of miR-130a-3p leads to sustained profibrogenic effects of macrophages. Interestingly, inhibiting miR-142-5p and increasing of miR-130a-3p expression has led to reduced fibrosis burden [25], the observation further indicating potential role of miRNA in pulmonary fibrosis.

Under-expression of miR-26 has been seen in A549 cell line and BLM mouse. miR-26 seems to play an important in the epithelial-mesenchymal transition (EMT), a key step in the repair and scaring. The upregulation miR-26 reduces the EMT via targeting HMGA2 (high mobility group AT-hook 2) [26]. Das et al., reported the reduced expression of miR-326 in lung tissue of IPF patients, while upregulation of this miRNA inhibits the expression of TGF-β1 and suppresses the fibrotic response by downregulating the profibrotic genes including MM9, ETS1, SMAD3 and overexpression of antifibrotic genes including SMAD7 [27].

Levels of miR-486-5p, which targets the SMAD2 gene and is a key mediator of pulmonary fibrosis, were found to be decreased in the lung tissues of IPF as well as in the silicosis patients. The overexpression of this miRNA, in animal model as well as BLM-mouse, significantly reduces the distribution as well as severity of pulmonary lesion [28]. miR-17 ~ 92 cluster and miR-200 family which has 6 and 5 species of miRNA, respectively, controls the susceptibility to cellular senescence in IPF [29]. In another study consisting two cohorts – hypersensitivity pneumonitis and NSIP patients, miRNA profiling of serum samples revealed a difference in the miRNA's expression between two study groups. miR-375 and miR-193a were overexpressed in NSIP while miR-374a, miR-18a, miR-15a, and miR-106b were found upregulated in hypersensitivity pneumonitis patients [30]. This signifies the role of miRNAs in pulmonary fibrosis associated with diseases other than IPF.

More recently, pulmonary fibrosis has been observed among significant number of patients following recovery from acute COVID-19 [31]. miRNAs have also been implicated in COVID-19 associated manifestations, including pulmonary fibrosis [31]. Some miRNAs, such as miR-17-5p, that plays a key role as an anti-viral molecule in pulmonary infections, have also been explored as potential therapeutic targets in COVID-19 [32]. miR-574–5p is an important negative regulator of pro-inflammatory response that inhibits TLR4/ NF-kB signaling and may halt the development and progression of acute respiratory distress syndrome (ARDS) [33]. ARDS is also characterized by the presence of inflammation and a subset of patients also develops fibrosis [34].

Current evidence suggests that both virus and host-derived non-coding RNAs play important roles in susceptibility and protection against Covid-19 infection. There is some study that delineate the differential expression profile of ncRNAs in Covid-19 [35]. A study by Farr et al., reported 55 miRNAs to be altered in early stages of Covid-19 patients (n = 10). Their results showed that miR-4742-3p, miR-31-5p and miR-3215-3p were the highly upregulated; and miR-776-3p and miR-1275 were strongly down-regulated. Additionally, by incorporating supervised machine learning, they found a 3-miRNA based signature

(miR-23a-3p, miR-423-5p and miR-195-5p) that classified Covid-19 cases independently [36].

Apart from above mentioned miRNAs, there are many other miRNAs which play important role in pulmonary fibrosis. The miRNAs implicated in IIPs and post-Covid fibrosis and their targets and functions are summarized in Table 1.

Circular RNAs

As mentioned previously, circRNAs are the covalently closed RNA molecules that are highly tissue specific, stable and play critical role in the regulation of gene expression of many essential genes involved in the various biological processes, including fibrosis.

In one study, RNA sequencing led to the identification of 74 differentially expressed circRNAs in BLM-induced pulmonary fibrosis in mice [55]. The study also demonstrated that circ949 and circ057 create a network with lnc556 and lnc865 and simultaneously regulate miR-29b-2-5p by targeting STAT3 phosphorylation [55]. These findings suggest that circRNAs work by interacting with other non-coding RNAs to regulate pulmonary fibrosis. [55] Another study, consisting of plasma sample of IPF patients, identified 67 dysregulated circRNAs – 38 overexpressed and 29 down-regulated transcripts. Most of these transcripts were generated from the exonic regions. The majority of the host genes of these circRNAs were involved in the cell cycle regulation, RNA transport, and adherens junctions. Moreover, ceRNA (competing endogenous) network of mRNAs/miRNAs/circRNAs specified that circRNA-protected mRNA participated in many signaling pathways including Wnt, JAK, TGF-β1, VEGF, MAPK etc. and could also functioned as pulmonary fibrosis biomarker [56].

Many circRNAs work by interacting with miRNA, such as circRNA_010567 which has a profibrotic function. The profibrotic action is partly mediated by miR-141/TGF- β1 [57]. TADA2A is a circRNA, that is downregulated in both the cell line and the primary human lung fibroblasts derived from IPF patients. Overexpression of circTADA2A suppresses the activation and proliferation of cell line derived from normal human lung fibroblast. circTADA2A represses the activation of lung fibroblasts via miR-526b/Cav1 and decreases the lung fibroblasts proliferation through miR-203/CaV2, that culminates in the suppression of excess deposition of extracellular matrix and ameliorates IPF [58].

In SiO2 mediated pulmonary fibrosis (silicosis) that involves the alveolar macrophages, the SiO2 particles stimulate different factors at the inflammatory sites which also include ncRNA [59]. In a study, circZC3H4 has been found to be elevated which positively correlates with the protein expression of ZC3H4 in the alveolar macrophage of the

Table 1 Table 1

miRNA	Expression	Target	Function	Biospecimen origin	Reference
miR-199a-5p	Upregulated	CAV1	Activation of Lung Fibroblast through TGF-β	lung tissue of IPF patients, BLM-mouse	[37]
miR-26a	Downregulated	HMGA2	Induces Epithelial to mesenchymal transition	BLM-mouse, A549 cells	[38]
miR-9-5p	Upregulated	TGFBR2	Inhibits pro-fibrogenic transformation of fibroblasts and prevent organ fibrosis	BLM mouse, IPF lung	[39]
miR-130a-3p	Downregulated	PPARγ	regulation of profibrotic gene in macrophages	BLM-mouse, IPF patient's macrophage	[40]
miR-21	Upregulated	ADAMTS-1	Increases Col1 and Col3 and promotes lung fibrosis	PB of IPF patients and BLM-Rat	[41]
miR-185, miR-186	Downregulated	COL5A1	EMT transition and Collagen V	IPF lung, A549 and HCC827 cells	[42]
miR-1307-3p	Upregulated	3' UTR of SARS-CoV-2, BCL2, PI3K	Suppression of endocytosis, exocytosis, proliferative, and diabetes signaling pathways	Lung tissue	[43]
miR-29c	Downregulated	Fas	Cessation of Fas mediated apoptosis	lung fibroblast, IPF lungs	[44]
miR-34a	Upregulated	SIRT1	Cellular senescence inhibition	Alveolar epithelial cell and lung fibroblast	[45]
miR-155	Upregulated	SHIP-1, liver X receptor, Mep1a	EMT transition, collagen synthesis	HU-VEC, NR8383 murine monocytes/macrophage cells, Mouse primary lung endothelial cells	[46–48]
miR-199	Upregulated	Caveolin-1	Promotes proliferation & differentiation	Mouse Model, MR-5, hFL1, A549, HEK-293	[49], [50]
miR-328	Upregulated	FAM13A	Promotes proliferation and increases the expression of PF markers	Rat-model, Macrophages, Lung fibroblasts	[51]
Let-7	Downregulated	LOX1 HMGA2	Reduces cell damage	Mouse MLE-12, A549, RLE-6TN Human lung samples	[52]
MiR-193	Downregulated	SHH	Increases autophagy and inhibits fibrinogen expression	Mouse, A549	[53]
MiR-708	Downregulated	ADAM17	Inhibits cell differentiation	Mouse A549, MRC-5 Human Lung Samples	[54]

silicosis patients. The protein expression of ZC3H4 is regulated by circZC3H4 via miR-212, which further activates the alveolar macrophages, these activated macrophages lead to the fibroblast proliferation and migration [60]. Another circRNA, circHECTD1, which is derived from the exonic region of the HECT gene, was found to be decreased in SiO2 induced macrophages, however, it was interestingly found to be accumulated in the lung tissues. Evidence suggests that circHECTD1 can competitively inhibit ZC3H12A ubiquitination with HECTD1 for ZCH3A12A protein and

affects the macrophage polarization and activation, and suppresses inflammation cascade [61]. Moreover, higher expression of circHECTD1 is also involved in the transition of endothelial and epithelial cells into mesenchymal cells [62]. In SiO2 exposed environment, the expression of circHIPK2 increases in the lung fibroblasts which interacts with miR-506-3p and induces ERS (sigma-1 receptor-associated endoplasmic reticulum stress) and exacerbate fibrosis progression [63].

Another study, showed that PPP1R13B gene derived circ-012091 was downregulated and negatively regulates the expression of PPP1R13B protein in the lung fibroblasts [64]. PPP1R13B is a key protein that plays a vital role in the proliferation and migration of fibroblasts through ERS stress and autophagy pathway. ERS can be induced through many factors such as viral infections, hypoxia and others. Afterward ERS induces apoptosis, epithelial to mesenchymal transition and inflammation that progresses into pulmonary fibrosis [64], [65].

Recently, Li et al., demonstrated that FOXO3 (a suppressor of fibroblast activation) binds with the promoter region of the SPON1 and selectively increases the expression of circSPON1. They also showed the involvement of circSPON1 in the ECM deposition in the normal human lung fibroblast cell line i.e., HFL-1. Further, the study showed that circSPON1 interacts with Smad3 which is induced by TGF-β and suppresses the fibroblasts activation via disruption of nuclear translocation [66].

miR-7 is believed to be a crucial fibrosis inhibitor that inhibits EMT transition by targeting TGF-β/Smad signaling pathway, while CDR1as may function as a profibrotic agent that acts via sponging miR-7 in A549 cell lines and bronchial epithelial cells of human [67].

Evidentially, acute lung injury can also lead to pulmonary fibrosis as a result of infection or any physical or chemical trauma [68]. In rat model, Ye et al., found ten differentially expressed circRNAs in BAL and tissue samples after smoke inhalation, indicating that circRNAs have an apparent role in smoke induced ALI and pulmonary fibrosis [69].

A bioinformatics-based study on Covid-19 revealed the differential expression of circRNA and lncRNA isolated form the blood sample of Covid-19 patients. Among 570 circRNA that were differentially expressed, 155 were upregulated and 415 were downregulated; while a total of 898 lncRNAs were differentially expressed, 414 and 484 genes upregulated and downregulated, respectively. Gene ontology and pathway enrichment analysis revealed that genes corresponding to these ncRNAs were mainly involved in the regulation of host cell immunity and inflammation, cell cycle, apoptosis, and substance and energy metabolism [70]. Table 2 provides a summary of important circRNAs as well as lncRNAs implicated in pulmonary fibrosis.

lncRNA

Another major class of non-coding RNA is lncRNA which is more than 200 nucleotides in length and the second most widely studied ncRNA in human diseases after miRNA. There are studies which have reported dysregulation of lncRNA in acute lung injury as well as pulmonary fibrosis [86], [87].

Epithelial cells are considered to be the initial site for microinjuries which lead to alteration in the cellular microenvironment, ECM deposition, and fibroblast activation [88], [89]. Using single-cell RNA-sequencing, Gokey et al., identified the 21 differentially expressed lncRNAs in the epithelial cells, lncMEG3 was the most significant [90]. Recent study has shown that lncMEG3 influences the differentiation of epithelial cells and increases their migration by regulating multiple genes, which include STAT3, KRT14, TP63, YAP1, and TGF-β [72][90].

A study by Fukushima et al., showed that dysregulation of Rbm7-lncNEAT1 axis, triggers the apoptosis of alveolar epithelial cells in Rbm7-deficient mice, non-hematopoietic (CD45−) cells, BLM-induced mice, and RBM7−/− HEK293 cells. The dying alveolar epithelial cells secrete chemokines which leads to the recruitment of atypical monocytes in the cellular microenvironment that drives pulmonary fibrosis [91]. lncTERRA also cause epithelial apoptosis and pulmonary fibrosis, however its mechanism is somewhat different from NEAT1. lncTERRA causes telomere attrition and mitochondrial dysregulation affecting genes associated with oxidative stress such as ROS, catalase, superoxide dismutase, genes associated with senescence regulators including P53 and mitochondrial genes (cytochrome c, caspase-3, caspase-9 and Bcl-2 family); all these genes are involved in the fibrosis process [92].

lncAP003419.16 is highly expressed in IPF patients and TGFβ1-treated epithelial cells. lncAP003419.16 drives pulmonary fibrosis by targeting RPS6KB2 dependent mTOR signaling pathway [93]. lncITPF is dysregulated in fibroblasts in IPF and human embryo. It is transcribed from its host gene ITGBL1 at 10th intron to the 11th exon, the expression of lncITPF is increased in the nucleus, suggesting that ITPF regulates the transcription of ITGBL1 that codes for TIED protein which is related to β integrin [94]. High ITGBL1 level has been associated with increased expression of fibrosis markers such as collagen, vimentin, and a-SMA. Although the fibrotic function of ITPF depends on its host gene, they do not share the same promoter, ITPF promoter is bound to smad2/3 while TGF-β1-smad2/3 was found to be the upstream inducer in the fibrotic pathway. Moreover, ITPF is also regulating the acetylation of H3 and H4 histone proteins in ITGBL1 promoter by targeting heterogeneous nuclear ribonucleoprotein L (hnRNP L).

Table 2 Summary of targets and functions of circRNAs and lncRNAs involved in pulmonary fibrosis

circRNA	Expression	Target	Function	Biospecimen	Reference
circ_406961	Downregulated	ILF2	Inhibitory effects on inflammation	PM2.5 treated BEAS-2B cells	[71]
circZC3H4	Upregulated	ZC3H4 protein via miR-212	Macrophage activation, fibroblasts proliferation and migration	Alveolar macrophage of silicosis patients	[60]
circHECTD1	Downregulated	ZC3H12A	M1/M2 polarization, inflammation initiation	Alveolar macrophage of silicosis patients	[61]
circHIPK2	Upregulated	miR-506-3p	induce sigma-1 receptor-associated endoplasmic reticulum stress	Lung fibroblast	[63]
circ-012091	Downregulated	PPP1R13B	Proliferation and migration of via ERS and autophagy pathway	Lung fibroblast	[64], [65]
LncRNA					
MEG3	Upregulated	TAT3, TP63, KRT14, YAP1	Enhances cell migration, tissue remodeling	IPF lung tissue	[72]
MALAT1	Downregulated	Hexokinases	Aberrant macrophage activation	IL-4 treated macrophage	[73]
NEAT1	Upregulated	Rbm7, BRCA1	Triggering of apoptosis	Rbm7-deficient mouse, bleomycin-induced fibrosis mouse, nonhematopoietic (CD45-) cells and RBM7−/− HEK293 cells	[74]
ITPF	Upregulated	ITGBL1	Act via TGF-β-Smad2/3-hnRNP L signaling pathway	BLM-mouse, TGF-β-treated fibroblast MRC-5 and blood samples from IPF patients	[75]
lncTERRA	Upregulated	Genes & component associated with telomeres and mitochondria	Regulates telomeric and mitochondrial functions	Blood from IPF patients, BLM-mouse, A549, MLE-12	[76]
lncR-PCF	Upregulated	mir-344a-5p	Promotes pulmonary fibrogenesis	IPF lungs, BLM-mouse, RLE-6TN cells	[77]
SIRT-AS	Upregulated	miR-34a	SIRT1-AS overexpression inhibited TGF-β-mediated EMT	BLM-mouse lung	[78]
ZEB1-AS1	Upregulated	miR-141–3p, collagen 1, fibronectin 1, α-SMA, E-cadherin, TGF-β1	ZEB1-AS1 through ZEB1-mediated EMT via binding miR-141–3p could promote pulmonary fibrosis.	BLM-mouse AEC type 2	[79]
HOTAIRM1	Downregulated	IL-17 signaling pathway	Regulates viral transcription and inflammatory development	Bronchoalveolar lavage fluid of COVID-19 patients	[80]
DANCR	Downregulated	REL, RELA, and NFkB1 and to AChE and IL-1b	Promoted infection	Inflammatory prone lung tissue	[81]
MALAT1, NEAT1	Upregulated	CAPN1	Inflammatory response	BALF, NHBE Cells	[82–85]

Analysis also revealed that ITPF is correlated with clinico-pathological characteristics of IPF patients [94].

lncRNA NONMMUT028949.2 or lnc949 is transcribed from FKBP5 (FK506 binding protein 5) gene and exerts its effect by suppressing FKBP5 expression post transcriptionally. lnc949 is present in the cytoplasm. The expression of lnc949 was found to be significantly upregulated in L929 cells treated with TGF-β1. Fibrosis biomarker such as collagen, vimentin as well as α-SMA were also enhanced in treated L929 cells. But, when the expression of lnc949 was inhibited by using small interfering RNA (si-lnc949), the expression of vimentin, α-SMA, and collagen reduced significantly. To reverse this condition, the expression of FKBP5 was inhibited using siRNA that leads to an increase in the expression of lnc929 as well as fibrosis markers, suggesting the regulatory role of lnc929 in the fibrosis process [55].

MALAT1 is a prominent lncRNA involved in many diseases including acute lung injury [87]. MALAT1 has been reported in macrophage activation and associated with pulmonary fibrosis. In differentially activated macrophages, the expression of MALAT1 is distinctly altered. The knockdown of MALAT1 leads to inhibition of LPS-induced activated M1 macrophage while in M2 type macrophage, knockdown of MALAT1 leads to increase in its expression via IL-4 pathway [95]. P65, a subunit of NF-kB can bind to the promoter

of MALAT1 in LPS-induced macrophages. It suggests MALAT1 is a direct transcriptional target of NF-κB activation. As opposed to LPS-stimulated macrophages, IL-4 dampened MALAT1 expression in macrophages. Overall, these results suggest that MALAT1 is involved in the differential activation of macrophages as a result of the distinct regulation of its expression by LPS and IL-4. On the other hand, downregulation of MALAT1, induces pro-fibrotic M2 macrophage differentiation activated by IL-4. It increases the expression of Arg-1 and YM-1, which leads to induction of oxidative phosphorylation, mitochondrial pyruvate carriers and enhancement in the oxygen consumption and mannose receptor C-type-1. These observations suggest that MALAT1 controls pulmonary fibrosis by triggering activation of macrophages [95].

Recently, MALAT1 has been implicated as one of the key lncRNA involved in the COVID-19 infection [96]. Upregulation of MALAT1 is reported in SARS-CoV-2 infected NHBE cells (bronchial) [96]. MALAT1 and NEAT1 are important immunomodulatory lncRNAs that are reported as highly differentially expressed lncRNAs among mild and severe COVID-19 patients across various cell types suggesting its role as a potential immune dysregulators during COVID-19 [97].

lncRNAs has been shown to have a role in silicosis associated pulmonary fibrosis. In silicotic rat lung, upregulated lncRNA LOC103691771 was found to be associated with macrophage activation and fibroblast differentiation through TGFβ1-Smad2/3 signaling pathway [98]. Ma et al., has shown that lncRNAs also involved in air-pollution related lung disease [99]. Authors reported that the lung tissue exposed to PM2.5 had a total of 309 differentially expressed lncRNAs, 201 upregulated and 108 downregulated. Among these upregulated lncRNA, it was discovered that Gm16410 regulates the TGF-β1/Smad3/p-Smad3 signaling pathway [99].

Age is an important risk factor in Covid-19 and is associated with the severity of the disease, older people are at higher risk of developing a more severe disease. Inflammaging is a term used to describe the hyperinflammatory symptoms of these older people. In a study of serum sample of 29 Covid-19 subjects, a set of 3 miRNAs i.e., miR-21-5p, miR-146a-5p, and miR-126-3p was found to be involved in the regulation of inflammaging [100]. miRNA has been shown to predict the response to tocilizumab, an anti-IL-6 drug, in COVID-19 patients with multifocal interstitial pneumonia. The results showed that subjects who did not respond to Tocilizumab and experienced the most adverse outcome, had lower serum levels of miR-146a-5p. BALF and PBMC samples also have shown several differentially expressed lncRNA molecules among patients with Covid-19. Most of these differentially expressed lncRNAs were mainly play

roles in immune related process and pathways. 3 lncRNAs viz., PVT1, HOTAIRM1 and AL392172.1 were amongst the most influential upregulated lncRNAs with high affinity for the SARS-CoV-2 genome binding, suggesting major regulatory role of lncRNAs during the infection [101].

Apart from these non-coding transcripts other ncRNAs such as siRNA, ceRNA are also been reported to play a key role in pulmonary fibrosis. Ahn et al. designed 13 siRNAs that mimics the miRNAs by implementing seed sequences from antifibrotic miRNAs and targets the SARS-CoV-2 to inhibit fatal lung fibrosis. Among those 13 siRNAs, one candidate siRNA 27/RdRP was functionally validated. Similar to miR-27, it targets the nsp12 region of the SARS-CoV-2 virus, and inhibits TGF-β-induced pulmonary fibrosis and COL1A1 (a collagen-producing gene) in human lung cells. Thus, implying the role of siRNA as a potential therapeutic target in COVID-19 associated pulmonary fibrosis [102].

Conclusions

A number of non-coding transcripts have been detected in studies involving IPF and Covid-19-associated pulmonary fibrosis. All three major subclasses of ncRNAs i.e., miRNA, lncRNA, and circRNA have been implicated in the pathogenesis of pulmonary fibrosis and shown as promising therapeutic targets. However, most of the data is based on *in-vitro* or animal models, and/or limited patient numbers with stringent selection criteria. Therefore, large-scale validation of these ncRNAs is imperative for assessing their potential as clinically useful diagnostic/prognostic marker/s and to check their potential as therapeutic targets.

Declarations

Conflict of interest None.

ethical approval This manuscript is a review article and thus does not require ethical approval.

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