Deciphering the crosstalk of noncoding RNAs in the progression of IPF

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Abstract
Idiopathic pulmonary fibrosis (IPF) is an agenogenic, rare, and lethal disease, with high mortality and poor prognosis and a median survival time as short as 3 to 5 years after diagnosis. No effective therapeutic drugs are still not available not only in clinical practice, but also in preclinical phases. To better and deeper understand pulmonary fibrosis will provide more effective strategies for therapy. Mounting evidence suggests that noncoding RNAs (ncRNAs) and their interactions may contribute to lung fibrosis; however, the mechanisms underlying their roles are largely unknown. In this review, we systematically summarized the recent advances regarding the crucial roles of long non-coding RNAs (lncRNAs), microRNAs (miRNAs), and circular RNAs (circRNAs) and crosstalk among them in the development of IPF. The perspective for related genes was well highlighted. In summary, ncRNA and their interactions play a key regulatory part in the progression of IPF and are bound to provide us with new diagnostic and therapeutic targets.

Keywords ncRNA · lncRNA · miRNA · circRNA · crosstalk · IPF

Introduction
IPF remains a chronic, debilitating, progressive pulmonary parenchyma illness, which falls under idiopathic interstitial pneumonia (IIP). High-throughput sequencing and bioinformatics analyses improve our understanding of IPF ranging from aging, protease systems, lipid peroxidation to signal transduction mechanisms [1]. Most IPF patients are sporadic, whereas familial pulmonary fibrosis (FPF) accounts for approximately 2 to 20% of cases, suggesting a gene-environment interaction in IPF [2]. Increasing evidence indicates a greater influence of genetic factors; however, the possible molecular mechanisms involved in IPF have not been fully identified. With the discovery of ncRNA in the 1960’s, we identified its involvement in gene expression at transcription or post-transcription level, through epigenetics. ncRNAs constitute 98% of the human genome and are transcribed from the genome, but do not encode proteins. It can be categorized into lncRNAs, miRNAs, circRNAs, and other ncRNAs that differ in structure, size, and function. ncRNAs can modulate protein abundance by modifying transcription, mRNA processing and mRNA stability. Presently, ncRNAs are considered important mediators for various physiological and biological reactions, like metabolism and differentiation and are also related to some pathological conditions [3]. Over the past years, researchers have discovered that different ncRNAs might be involved in different diseases like diabetes, cancer, atherosclerosis, etc. [4]. Understanding the function of ncRNAs may elucidate the mechanisms underlying the pathogenesis of IPF, possible biomarkers for this disease, and novel approaches for IPF therapy.

Whether ncRNAs interact with each other in IPF remains a mystery, with relevant data being sparse and non-systematic. In this review, we systematically and comprehensively discuss the effect of ncRNAs on IPF pathogenesis and prognosis and how the crosstalk within ncRNAs influences the development of IPF. However, these results still need further experimental validation and identification.

The recent advances of ncRNA in IPF

The effect of lncRNAs on IPF

lncRNAs are a kind of ncRNA that lack an open reading frame, are longer than 200 nucleotides and do not encode proteins. It was discovered by Okazaki et al. [5] and is
located in the nucleus or cytoplasm. Non-coding RNAs can be grouped into six species based on the position in the genome, namely, exon sense-overlapping lncRNA, intron sense-overlapping lncRNA, intronic antisense lncRNA, natural antisense lncRNA, bidirectional lncRNA and large intergenic noncoding RNA (lincRNA) [6, 7]. In human, more than 15,000 lncRNAs have been defined with the rapid development of molecular biology technology, many of which play a potential role in normal physiology and human disease. Some lncRNAs are considered valuable biomarkers for certain cancers, cardiovascular diseases, and lung disorders during diagnosis and therapy. Cao et al. [8] discovered that, for the first time, 210 lncRNAs were upregulated while 358 were downregulated in murine bleomycin-induced fibrosis. This suggesting these aberrant-expression lncRNAs significantly alter the ultrastructure of lung tissue, laying the foundation for future research on the molecular targets of lncRNAs. However, the number of lncRNAs involved in IPF and their effects have not been fully described. Mounting research exist on lncRNA in the pathogenesis mechanism of IPF. lncRNAs can regulate gene expression through transcription, epigenetics and post-transcription processes [6]. Studies show that lncRNA might participate in a series of important procedures, like X-chromosome inactivation, gene imprinting, transcriptional activation and interference etc. [9]. Interestingly, in bleomycin-induced mice models, lncRNAs are found to be related to many signaling pathways, like the chemokine and JAK/STAT signal transduction pathway [8]. lncRNAs can affect the expression of target or adjacent genes and involve inflammation-immune responses and telomere-mitochondrial function., playing a more complex part in IPF.

IncRNAs can regulate target or adjacent gene in IPF

LncRNAs function according to different action modes and can act as ceRNA of miRNAs, by absorbing specific miRNA and regulating the expression of the target gene. In other words, lncRNA acts as a miRNA “sponge” which prevents miRNA from binding to its targets. The expression of many lncRNAs strongly relates to their neighboring genes, which means they can function as cis-regulators. lncRNA transcription may influence adjacent genes in mostly positive or negative manners [10]. In fibroblasts, lncRNA RP11-413M3.4 promotes the upregulation of the adjacent gene Notch1, induces the proliferation and differentiation of myofibroblasts and produces a large amount of collagen fibers, leading to pulmonary fibrosis [11]. Song et al. [12] indicated that IncITPF can increase the expression of its nearby host gene, Itgβ1, through TGF-β1. The expression of lncRNA AP003419.16 and its adjacent gene RPS6KB2, is increased significantly in patients with IPF. More importantly, AP003419.16 might increase the possibility of aging-associated IPF [13]. The lncRNA, CDKN2B-AS1, appears down-regulated in IPF patients compared with healthy controls. Its adjacent gene, CDKN2A, which promotes lung cancer formation via the p53-signaling pathway, is also downregulated in IPF patients [14]. Additionally, the lncRNAs uc.77 and 2700086A05Rik can cause EMT by regulating the adjacent genes, Zeb2 and Hoxa3, in paraquat-induced pulmonary fibrosis in experimental mice [10].

IncRNAs are involved in IPF through the inflammation-immune response and telomere-mitochondrial function

Evidence of immune inflammatory damage has been found in many IPF cases. An up-to-date study revealed that the upregulation of certain lincRNAs, namely LINC00960 and LINC01140, and knockdown of LINC01140 but not LINC00960, stimulates the inflammatory response in IPF fibroblasts. Thus, demonstrating the importance of lincRNAs as regulators of proliferation and inflammation in IPF for the first time [15]. Dai et al. [16] found that the lncRNA MALAT1 could activate the lipopolysaccharide-induced inflammatory response pathway and promote the progression of lung injury in rat models. lncRNAs located in telomeres can partially explain the cause of IPF, specifically lncRNA Telomeric repeat-containing RNA (TERRA). The regulatory mechanism of TERRA in IPF pathogenesis was identified in Gao’s research [17]. This suggested that the abnormal expression of TERRA in ILD cases is sensitive to oxidative stress or apoptosis in alveolar epithelial type 2 cells. Cao et al. [8] also found differences in expression of lncRNA RMRP and telomeres enzyme RNA component (TERC) in a bleomycin-induced fibrotic murine model. The destruction of the CCAAT box in the lncRNA TERC promoter can induce pulmonary fibrosis [18]. Moreover, Liu et al. [19] found that the inactivation of lncRNA TERT reduces the severity of pulmonary fibrosis in conditional knockout mice.

Research status of miRNA in IPF

miRNAs serve as early diagnostic biomarkers and therapeutic targets for IPF

Different from lncRNAs, miRNA is a class of single-stranded ncRNAs with only 19–25 base pairs, guiding the effector to miRNAs to repress protein production [20]. It can directly bind to the 3’ untranslated region (3’ UTR) of its target gene to control gene expression. To date, researchers have identified more than 3700 statistically significant human mature miRNAs and acquired 3494 new precursors [21].
miRNA may be a diagnostic biomarker for IPF and can also determine its prognosis [22]. Abnormal changes of miRNA expression not only show in peripheral blood but also in lung biopsy samples of IPF patients. Previous investigations have indicated that the miR-17-93 gene cluster (miR-145, miR-199-5p, miR-200 and miR-154) is abnormally expressed in human IPF tissues. In patients, miR213p is up-regulated obviously, whereas miR630 is down-regulated. Furthermore, animal model experiments have demonstrated that inhibition of the miR-17-92 gene cluster (miR-29, miR-145, miR-199-5p, and miR-200) expression levels can affect the progression of pulmonary fibrosis [23]. Yang et al. [24] indicated that 47 miRNAs differed in expression, with 21 being upregulated and 26 downregulated. Surprisingly, over 80% of miRNAs are decrease in IPF cases. Apart from this, mir-21/mir-126 is upregulated and mir-672/ mir-143 downregulated in asthmatic mice models [25]. Different miRNA expression profiles could not only distinguish between cancers and non-cancers, but also different subtypes of lung cancer [26, 27]. However, the function of miR-26a in COPD is still unclear [28]. Differential expression of miRNA is observed when comparing slow-progressing with rapid-progressing IPF [29]. The content of miR-21, miR-155 and miR-101-3p correlates with IPF development, indicating their potential use in determining the prognosis of IPF [30]. This shows that miRNAs can be novel diagnostic indicators for respiratory diseases, particularly IPF.

As previously discussed, the expression differences of miRNAs can lead to respiratory diseases, especially IPF. In a previous study, SPC3649, an LNA-modified complementary oligonucleotide that can bind to miR-122, is used to repress hepatitis C virus (HCV) viremia. This may be the first use of targeted miRNAs for treatment [31]. Experimentally, it has been found that inhibiting miR-21 in mice with renal fibrosis proportionately relieves the degree of renal injury [32]. The findings of Kota et al. [33] postulate the possibility of utilizing miR-26a for treating liver cancer. More relevant to our investigation, miR-486-5p may be a therapeutic target for pulmonary fibrosis [34]. Previous investigations have only identified miR-489 as a therapeutic intervention in the maturation of pulmonary fibrosis, induced by silica in mice. However, epigenetic modifying drugs for non-neoplastic lung diseases, like miRNAs, is at its beginning with initial preclinical animal models. Verification with further clinical studies is still required to validate their utility.

miRNAs involved in the pathogenesis mechanism of IPF

Gene regulation with lncRNAs is complex and difficult to study. miRNAs mainly regulates negatively the expression of their target genes at the post-transcriptional level through mRNA destabilization or/and degradation. Not only does miRNA play a significant part in cell proliferation and differentiation, but also in the mechanism of IPF pathogenesis. They can also be involved in IPF lung epithelial repair, EMT, fibroblast activation, myofibroblast differentiation, macrophage polarization, alveolar epithelial cells (AEC) senescence, and collagen production [22]. Every miRNA can complement and bind to many different target genes and different miRNAs can also act on the same gene. MiR-29c can bind to the 3′ UTR of Foxo3a and regulate AEC update and apoptosis to hinder IPF [35]. MiR-26a can bind to its target, HMGA2, which transforms lung epithelial cells into myofibroblasts in mice model with bleomycin-driven fibrosis. It provides evidence that miR-26a takes on an essential part in the pathology of IPF through the EMT mechanism [36]. Moreover, miRNAs like miR-375, miR-200, and let-7d participate in IPF by regulating EMT. Additionally, miR-21, miR-26a, miR-155, miR-9-5p, and miR-27a-3p participate in the course of IPF by regulating fibroblast function [28]. MiR-145 adjusts myofibroblast function in bleomycin-induced pulmonary fibrosis [37]. In another study, Wang and colleagues found that miR-34a not only promotes the expression of β-galactosidase, but also inhibits cell proliferation [38]. MiR3245p can activate ROCK-1 and ROCK2, which are involved in cell proliferation, differentiation, apoptosis, adhesion, motility, and ECM remodeling in mouse fibrosis models [39]. MiR-29 can regulate ECM through its target genes; COL1A1-A2, ELN, FBN1, and even COL3A1 [40]. Another target gene of miR3245p, namely ITGB1, inhibits collagen formation, EMT, and myofibroblast mobility in the lung tissues of bleomycin-induced mice models. Notably, miRNAs can regulate each other by complementarily binding to each other during the pathogenesis of diseases. Early literature states that that miR-26a and let-7d collaboratively attenuate pulmonary fibrosis [41]. Additionally, miRNAs can be involved in pulmonary fibrosis through methylation and the regulation of early inflammation after lung damage. For example, the miR-17-92 cluster promoter is hypermethylated in IPF [42]. A summary of the miRNAs and their targets in IPF is illustrated in Table 1.

The role of circRNA in the development of IPF

Contrary to linear RNA, circRNA is derived from a single RNA molecule, the ends of which are formed with covalent linkage rather than 5′ and 3′ free ends, is resistant to RNase R, and thus remains more stable than linear RNA. Initially, circRNA was believed to be “errors” or “faults” of RNA splicing. It is, however, part of the novel category of endogenous RNAs, more widespread and diverse in mammals than previously thought [43]. circRNA accounts for a considerable proportion of the transcript. Abundant circular molecules exceeds its counterpart of linear miRNAs by at least tenfold [44]. Sanger et al. [45] was the first to discover circRNA, subsequently followed by the
discovery of DCC, ETS-1, SRY, cytochrome P450 2C24, and cANRIL, in succession [46]. Memczak et al. [47] have identified 2000, 1900, and 700 circular RNAs in humans, mice, and nematodes from the sequencing data, respectively. However, the amount of circRNAs is probably much higher, as only reads spanning the back-splice sequence can be used for detection. Advances in RNA sequencing (RNA-seq) techniques have thus far led to the discovery of more than 100,000 types of circRNAs [44]. circRNAs can be grouped into three categories, namely, exonic circRNAs (ecircRNAs), circular intronic RNAs (ciRNAs) and exonic-intronic circRNAs (EIciRNAs). circRNAs mainly belong to annotated exons (86.6%) and are located in the cytoplasm. Only a small proportion of circRNAs originate from introns. It often displays tissue and developmental-stage-specific expression, playing a pivotal role in fine-tuning the regulation of post-transcriptional gene expression. More importantly, cells can secrete circRNAs into peripheral blood through exosomes. circRNAs commonly exist in exosomes, saliva, and blood. Based on their abundance, cell-type and tissue-specific expression and functions, circRNAs are recognized as emerging biomarkers in many diseases. The expression of circRNA is associated with many diseases, like atherosclerotic vascular disease, cancer, neurodegenerative diseases, and diabetes. They are also differentially expressed not only in colorectal cancer (CRC), but also in pancreatic ductal adenocarcinoma (PDAC) [48]. For example, the expression of circANRIL increases the risk of coronary heart disease and circRNA MYLK, as a ceRNA, promotes bladder cancer [49]. Researchers have discovered that the interaction of two molecules, ciRS-7 and miR-7, is associated with neural diseases [50]. In islet cells, CDR1as can interact with miR-7 and its targets to regulate the transcription, synthesis and secretion processes of insulin [51]. They indicate distinct positions in the diagnosis, treatment and prognosis of diseases. However, the effect of circRNA on IPF is little known for us.

Exceptional circRNA expression in IPF has been identified with highthroughput microarray assays. Li et al. [52] discovered that hsa_circRNA_100906, 102100 and 102348 are upregulated, while hsa_circRNA_101225, 104780 and 101242 are downregulated in IPF. circRNAs regulate RNA transcription [53], act as protein sponges [54], interact with proteins [55], translate proteins [56, 57] and can be used as miRNA sponges [58, 59] to affect cell behavior. However, the specific function and mechanism of circRNA in IPF has not been explicitly described as yet. In this study we provided valuable insights into the pathogenesis of circRNA in IPF. André et al. [60] revealed that BARD1, the host gene of hsa_circRNA_102910, can be involved in lung epithelial cell damage and fibroblast proliferation in IPF. The target gene of hsa_circRNA_102100 and 102101 may be related to chromosomal aneuploidy integrity and flawed cell cycles in IPF [61]. Zinc finger MYM-type 2, the host gene of hsa_circRNA _101225, can be involved in IPF by binding to fibroblast growth factor receptor1 [62]. The target gene of circRNAhsa_circ_104310 can affect

| miRNAs | Targets | Functions | Quotation |
|--------|---------|-----------|-----------|
| miR-213p | Not clear | Upregulation | [23] |
| miR-630 | Not clear | Downregulation | [23] |
| miR-29c | Foxxo3a | AEC renewal and apoptosis | [35] |
| miR-26a | HMGA2 | EMT and fibroblast regulation | [23, 36] |
| miR-200 | Not clear | EMT | [28] |
| Let-7d | Not clear | EMT | [23] |
| miR-375 | Not clear | EMT | [23] |
| miR-21 | Not clear | Fibroblast regulation | [23] |
| miR-155 | Not clear | Fibroblast regulation | [23] |
| miR-27a-3p | Not clear | Fibroblast regulation | [23] |
| miR-9-5p | Not clear | Fibroblast regulation | [23] |
| miR-145 | Not clear | Myofibroblast differentiation | [37] |
| miR-34a | Not clear | Promotes the expression of senescence markers and inhibits cell proliferation | [38] |
| MiR3245p | ROCK1/2, ITGB1 | Cell proliferation, differentiation, apoptosis, adhesion, motility, and ECM remodeling | [39] |
| miR-29 | ELN, FBN1, COL1A1, COL1A2, COL3A1 | ECM | [40] |
| miR-17–92 cluster | DNMT-1 | Methylation | [42] |

Table 1 The targets and functions miRNAs involved in IPF
the expression of the most genes in a transacting form
[63]. The host gene of hsa_circRNA_102348 may encode
a general binding partner, or chaperone, and regulate the
JAK/STAT signaling pathway [64].

The IncRNA-miRNA interaction network
promotes IPF

IncRNAs are not sufficient templates for protein transcrip-
tion but are involved in epigenetic regulation through miR-
NAs [65]. IncRNAs probably entangle with miRNAs and
influence its expression. In our study, we attempted to
ascertain the relationship between IncRNA and miRNA
and its function in pulmonary fibrosis. IncRNA can act on
miRNA in four ways. Firstly, IncRNAs may act as ceRNA
which plays a “molecular sponge” role in miRNA. For
example, mir-15a antagonizes the function of IncRNA
PFAR, which gives rise to extracellular collagen depo-
sition, fibroblasts proliferation, migration and differenti-
ation. Suggesting that IncRNA PFAR can act as sponge
for miR-15a, contributing to fibrogenesis in lung fibro-
blasts [66]. A similar mechanism occurs between IncRNA
NONMMUT065582 and mir-138, and IncRNA NON-
MMUT022554 and mir-26a, during lung fibrosis [67,
68]. The knock-down of IncRNA H19 diminishes lung
pulmonary fibrosis by binding to mir-140, suggesting
that H19 acts as sponge for miR-140 [69]. Meanwhile,
H19 can play a molecular sponge role for miR-196a and
miR-29b [70, 71]. The IncRNA, DNM3OS (dynamin 3
opposite strand) and its relevant miRNA, display differ-
ential expression in experimental or clinical conditions
[72]. IncRNA NONMMUT021928, designated as a pul-
monary fibrosis-associated IncRNA (PFAL), promotes
cell propagation, migration, motility and fibroblast-myo-
fibroblast transition processes by competitively binding to
miR-18a [73]. The Inc-PCF accelerates the propagation
of epithelial cells through the complementary binding of
miR-344a-5p, which has the target gene map3k11 [74].
IncRNA MRAK088388 “sponges” miR-29b-3p to regu-
late N4bp2, whereas MRAK081523 binds to let-7i-5p to
regulate Plxna4 in lung fibrosis [75]. Secondly, some
IncRNAs can be generated as precursor molecules of miR-
NAs. For example, IncRNA H19 can generate miR-675
[76]. Thirdly, IncRNA and miRNA compete for target
gene binding, therefore attenuating the inhibitory effect
of miRNA on target genes and increasing its stability. Lastly,
IncRNA can also regulate the expression levels of miRNA
by binding with other proteins.

miRNAs can also act on IncRNAs in two ways. Firstly,
miRNA accelerates the degradation of “molecular sponge”
IncRNA. In other words, miRNA can regulate the stabil-
ity or expression of IncRNA. When IncRNA-UCA1 binds
to miR-216b, its half-life is significantly shortened, indi-
cating that miR-216b accelerates the degradation of the
IncRNA-UCA1 molecule. Additionally, the inhibitor of
miR-216b can prolong the half-life of the IncRNA-UCA1
molecule and enhance its stability [77]. Secondly, miR-
NAs regulate the expression of IncRNA by regulating
the methylation of IncRNA promoters. A summary of the
IncRNAs and their targets in IPF is shown in Table 2.

Table 2 The targets and functions of IncRNAs involved in IPF

| IncRNA | Adjacent gene/target | Function | Quotation |
|--------|----------------------|----------|-----------|
| RP11-413M3.4 | Notch1 | Promote the proliferation and differentiation of myofibroblasts and produce a large amount of collagen fibers | [11] |
| ITPF | Itgb1 | Increase the risk of age-associated IPF | [12] |
| AP003419.16 | RPS6KB2 | Low expression in IPF predicts lung cancer | [13] |
| CDKN2b-AS1 | CDKN2A | Decrease in EMT | [14] |
| uc.77 | Zeb2 | EMT | [10] |
| 2700086A05Rik | Hoxa3 | EMT | [10] |
| PFAR | mir-15a | Extracellular collagen deposition, fibroblast proliferation, migration, and differentiation | [66] |
| NONMMUT065582 | mir-138 | | [67] |
| NONMMUT022554 | mir-26a | | [68] |
| H19 | mir-140/-196a/-29b | Promote fibroblast proliferation and epithelial-mesenchymal transition of alveolar epithelial cells | [69–71] |
| DNM3OS | Not clear | | [72] |
| NONMMUT021928 | mir-18a | Promote cell proliferation, migration and fibroblast- myofibroblast transition | [73] |
| Lnc-PCF | mir-344a-5p | Promote the proliferation of epithelial cells | [74] |
| MRAK088388 | mir-29b-3p | Upregulation | [75] |
| MRAK081523 | let-7i-5p | Upregulation | [75] |
circRNA acts on miRNA in the pathogenesis of IPF

circRNAs can also interact with miRNAs and influence their expression. Reports have stated that interactions between circRNA and miRNA undertake pathophysiolog-ical significance. The circRNA/miRNA regulatory network is involved in many signaling pathways of lung fibrosis, like transforming growth factor (TGFβ1) and NF-κB, which effects cell propagation, motility, migration and collagen compound in IPF [43]. We will explain the interaction between circRNA and miRNA from the following two aspects:

Firstly, circRNAs can sponge miRNAs to regulate transcription or affect parental gene expression, which is the principle function. circRNAs form part of a potent group of ceRNA molecules, including lncRNAs, pseudogenes and mRNAs, which all competitively bind to miRNAs. circRNAs may be more capable of binding to miRNAs than other ceRNAs as they are abundantly expressed in the cytoplasm and remain stable in cells. Tens of thousands of circRNAs have been found to compete with other RNAs for miRNA binding sites, based on the bioinformatics analysis, with only a few circRNAs being verified [78]. For example, CiRS-7, more specifically CDR1as, has been found to serve as a sponge for miRNA [79]. The reduced gene polymorphisms of miRNA binding sites in circRNA suggests it may play a regulatory role as a sponge for miRNA [78]. An exon circRNA with 1.2 kb, derived from the mammalian sex determination gene, may serve as a miR-138 sponge in the regulating process [57]. Furthermore, hsa_circRNA_100906 can bind to miR3245p/miR3305p and hsa_circRNA_102348 can directly interact with miR630, both of which are downregulated in IPF [73]. Zhang et al. [79] reported that miR3385p matches with hsa_circRNA_101996 and 102100 to regulate the coding gene CDC27, in IPF. Hsa_circRNA_101996 can act as the molecular sponge of miR9 and 145, to regulate lung fibrosis via several signaling pathways, like the plateleterived growth factor receptor β (PDGFR-β) pathway [80, 81]. Also, circRNA_102348 is upregulated and proves to directly interact with miR630 in IPF [73]. Is the sponge function of circRNAs a universal phenomenon? In an early investigation, several circRNAs bind to a particular miRNA through multiple binding sites. However, most circRNAs bind only to 1–2 binding sites on miRNA [82]. As mentioned, the CDR1as and SRY have more than 70 miR-7 and 16 miR-138 binding sites, respectively [43]. circRNAs with more than 10 miRNA-binding sites are very few [83]. Owing to the relative distribution of binding sites, some circRNAs lack the function of miRNA sponges [84]. Therefore, only a small number of circRNAs can function as miRNA sponges.

Instead of acting as a repository for miRNAs, circRNAs may also be involved in their intracellular transport. They are speculated to function as miRNA transporters, possibly even releasing their cargo by cleavage of a perfectly complementary miRNA [85]. As a typical example, CDR1as can transport miR-7 to a target location where miR-671 can stimulate the release of its load. At the same time, miR-7 targets PAK1 and FAK1, verifying the abovementioned assumptions [86, 87].

These results prove that circRNAs can form a series of post-transcriptional regulatory factors through its interaction with miRNAs. Compared with linear RNAs, more stable circRNAs are particularly attractive for researchers who concentrate on biotechnological and therapeutic applications. A summary of the circRNAs and their targets in IPF is shown in Table 3.

Systems biology and the related models

As IPF is a complicated dysfunctional in biological system, we can adopt systems biology approach to IPF studies. Systems biology involves both collecting high-dimensional data, which derive from noncoding RNAs findings, genomics, proteomics, epigenetic changes, metabolisms, and analyzing them in an integrated manner consisting of network

| circRNAs       | Targets       | Functions                                                                 | Quotation |
|----------------|---------------|---------------------------------------------------------------------------|-----------|
| circRNA_100906 | miR3245p/3305p| Downregulation in IPF                                                     [73]     |
| circRNA_102101| miR3385p      | Regulate the coding gene (CDC27)                                           [79]     |
| circRNA_101996| miR9 and 145  | Regulate lung fibrosis via PDGFRβ pathway                                  [80, 81] |
| circRNA_102348| miR630        | Encode a general binding partner, or chaperone, and regulate the JAK/STAT signaling pathway [64, 73] |
| circRNA_102910| Not clear     | Involved in lung epithelial cell damage and fibroblast proliferation       [60]     |
| circRNA_101225| Not clear     | Binding to fibroblast growth factor receptor1                             [62]     |
| circRNA_104310| Not clear     | In a transacting form to affect the expression of most genes              [63]     |
and modeling approaches. In this way, we could further our understanding of the IPF pathogenesis [88]. In one study, regulatory gene expression networks were identified using linear mixed-effect models and dynamic regulatory events miner (DREM). DREM generated a systems biology model that identified progressively divergent gene expression tracks with microRNAs and transcription factors that specifically regulate mild or advanced fibrosis [89]. Lorenzo-Salazar et al. [90] performed target-enriched sequencing on 11p15.5, 14q21.3 and 17q21.31 loci and found that 36 SNVs were associated with IPF susceptibility. In another prior study, 2D electrophoresis and mass spectrometry were used to compare protein patterns [91]. Allen et al. [92] conducted genome-wide analyses and identified KIF15, MAD1L1 and DEPTOR were association with IPF susceptibility. Todd et al. [93] applied aptamer-based proteomics to analyze plasma at enrolment. Linear regression model was used to determine differential protein expression while multivariable models were used to select proteins distinguished IPF from controls accurately.

**Conclusion**

Collectively, ncRNAs (including IncRNA, miRNA, and circRNA) can interact with each other to regulate the progression of lung fibrosis by means of a complicated network. This helps explain the treatment limitations of lung fibrosis over many years, while simultaneously providing a potential therapeutic strategy. IPF relates to multiple genes. Genetic variants, both rare (defined as having a minor allele frequency of less than 0.1%) and common (those with an allele...
frequency of more than 5%), are not only connected with sporadic pulmonary fibrosis, but also FPF. Certain genetic loci seem to be involved in complicated physiological processes, like alveolar stability, host cell defense, cell-cell barriers and cell senescence. Several common variants are also related to characteristic clinical phenotypes [94]. Definitive evidence supports this view that some single nucleotide polymorphisms (SNPs), as well as some common variants like MUC5B and TOLLIP are related to the susceptibility and prognosis of IPF [95]. Seven telomere-related genes (TERT, DKC1, RTEL1, NAF1, PARN, TINF2, and TERC) have been identified in adult-onset FPF so far [96]. Petrovski et al. [97] have also identified a relationship between TERT, RTEL1, and PARN and sporadic IPF. Further developments in genomic sciences will help identify other genes related to IPF in the next few years, providing new pathways for further research.

ncRNAs mainly include IncRNAs, miRNAs and circRNAs, each of which drive the progression of IPF. Additionally, ncRNAs can interact with each other in the pathogenesis of lung fibrosis. Therefore we have decrypted the crosstalk of ncRNAs in the progression of IPF systematically and integrally. A summary of interplay among ncRNAs in the development of IPF is shown in Fig. 2, the crosstalk among ncRNAs is summarized in Fig. 1.

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Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

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References

1. Ding Q, Luckhardt T, Hecker L, Zhou Y, Liu G, Antony VB, deAndrade J, Thannickal VJ (2011) New insights into the pathogenesis and treatment of idiopathic pulmonary fibrosis. Drugs 71:981–1001. https://doi.org/10.2165/11591490-000000-00000

2. Kropski JA, Blackwell TS, Loyd JE (2015) The genetic basis of idiopathic pulmonary fibrosis. Eur Respir 45: 1717–1727. https://doi.org/10.1183/09031936.00163814

3. Vemuganti R (2013) All’s well that transcribes well: non-coding RNAs and post-stroke brain damage. Neurochem Int 63(5):438–449. https://doi.org/10.1016/j.neuint.2013.07.014

4. Bayoumi AS, Sayed A, Broskova Z, Teoh JP, Wilson J, Su H, Tang YL, Kim IM (2016) Crosstalk between long noncoding RNAs and MicroRNAs in health and disease. Int J Mol Sci 17(3):356. https://doi.org/10.3390/ijms17030356

5. Okazaki Y, Furuno M, Kasukawa T (2002) Analysis of the mouse transcriptome based on functional annotation of 60,770 full-length cDNAs. Nature 420(6915):563–573. https://doi.org/10.1038/nature01266

6. Mercer TR, Dinger ME, Mattick JS (2009) Long non-coding RNAs: insights into functions. Nat Rev Genet 10(3):155–159. https://doi.org/10.1038/nrg2521

7. Ponting CP, Oliver PL, Reik W (2009) Evolution and functions of long noncoding RNAs. Cell 136(4):629–641. https://doi.org/10.1016/j.cell.2009.02.006

8. Cao G, Zhang J, Wang M, Song X, Liu W, Mao C, Lv C (2013) Differential expression of long non-coding RNAs in bleomycin-induced lung fibrosis. Int J Mol Med 32(2):355–364. https://doi.org/10.3892/ijmm.2013.1404

9. Wilusz JE, Sunwoo H, Spector DL (2009) Long noncoding RNAs: functional surprises from the RNA world. Genes Dev 23(13):1494–1504. https://doi.org/10.1101/gad.180909

10. Paraskevopoulou MD, Georgakilas G, Kostoulas N, Reczko M, Maragkakis M, Dalamagas TM, Hatziioannou AG (2013) DIANA-LncBase: experimentally verified and Computationally predicted microRNA targets on Long noncoding RNAs. Nucleic Acids Res 41:D239–D245. https://doi.org/10.1093/nar/gks1246
11. Guo H (2018) LncRNA RP11-413M3.4 regulates Notch1 in the pathogenesis of idiopathic pulmonary fibrosis. Dissertation, Shanxi Medical University (In Chinese)

12. Song XD, Xu P, Meng C, Song C, Blackwell TS, Li R, Li H, Zhang J, Lv C (2019) LncITPF promotes pulmonary fibrosis by targeting hnRNP-L depending on its host gene ITGBL1. Mol Ther 27(2):380–393. https://doi.org/10.1016/j.molther.2018.08.026

13. Hao X, Du Y, Qian L et al (2017) Upregulation of long non-coding RNA AP003419.16 predicts high risk of aging-associated idiopathic pulmonary fibrosis. Mol Med Rep 16(6):8085–8091

14. Du Y, Hao X, Liu X (2018) Low expression of long non-coding RNA CDKN2B-AS1 in patients with idiopathic pulmonary fibrosis predicts lung cancer by regulating the p53-signalling pathway. Oncol Lett 15(4):4912–4918. https://doi.org/10.3892/ol.2018.7910

15. Hadjicharalambous MR, Roux BT, Csomor E, Feghali-Bostwick CA, Murray LA, Clarke DL, Lindsay MA (2019) Long intergenic non-coding RNAs regulate human lung fibroblast function: implications for idiopathic pulmonary fibrosis. Sci Rep 9(1):6020. https://doi.org/10.1038/s41598-019-42292-w

16. Dai L, Zhang G, Cheng Z, Wang X, Jia L, Jing X, Wang H, Zhang R, Liu M, Jiang T, Yang Y, Yang M (2018) Knockdown of IncRNA MALAT1 contributes to the suppression of inflammatory responses by up-regulating miR-146a in LPS-induced acute lung injury. Connect Tissue Res 59(6):581–592. https://doi.org/10.1080/03008207.2018.1439480

17. Gao Y, Zhang J, Liu Y, Zhang S, Wang Y, Liu B, Liu H, Li R, Lv C, Song X (2017) Regulation of TERRA on telomeric and mitochondrial functions in IPF pathogenesis. BMC Pulm Med 17(1):163. https://doi.org/10.1186/s12890-017-0516-1

18. Aalbers AM, Kajigaya S, van de Hueil-Eibrink MM, van der Velden VH, Calado RT, Young NS (2012) Human telomere dysfunction reveals evidence for the expression of numerous novel pri-miRNAs in rapidly progressing idiopathic pulmonary fibrosis. Cell Death Dis 5:e1238. https://doi.org/10.1038/cddis.2014.207

19. Li H, Gu Y, Li T, Zhang Y, Huangfu L, Hu M, Zhao D, Chen Y, Liu S, Dong Y, Li X, Lu Y, Yang B, Shan H (2014) Integrated analyses identify the involvement of microRNA-26a in epithelial-mesenchymal transition during idiopathic pulmonary fibrosis. Cell Death Dis 5:e1238. https://doi.org/10.1038/cddis.2014.207

20. Yang G, Yang L, Wang W, Wang J, Wang J, Xu Z (2015) Discovery and validation of extracellular/circulating microRNAs during idiopathic pulmonary fibrosis disease progression. Gene 562(1):138–144. https://doi.org/10.1016/j.gene.2015.02.065

21. Li H, Zhao X, Shan H, Liang H (2016) MicroRNAs in idiopathic pulmonary fibrosis: involvement in pathogenesis and potential use in diagnosis and therapeutics. Acta Pharmacuetica Sinica B 6(6):531–539. https://doi.org/10.1016/j.apsb.2016.06.010

22. Li H, Zhao X, Shan H, Liang H (2016) MicroRNAs in idiopathic pulmonary fibrosis: involvement in pathogenesis and potential use in diagnosis and therapeutics. Acta Pharmacuetica Sinica B 6(6):531–539. https://doi.org/10.1016/j.apsb.2016.06.010

23. Chen X, Ba Y, Ma L et al (2008) Characterization of microRNAs in serum: a novel class of biomarkers for diagnosis of cancer and other diseases. Cell Res 18(10):997–1006. https://doi.org/10.1038/cr.2008.282

24. Lam TK, Shao S, Zhao Y, Marincola F, Pesatori A, Bertazzi PA, Caporaso NE, Wang E, Landi MT (2012) Influence of quercetin-rich food intake on microRNA expression in lung cancer tissues. Cancer Epidemiol Biomark Prev 21(12):2176–2184. https://doi.org/10.1158/1055-9965.EPI-12-0745

25. Liu T, Yu H, Ding L, Hu M, Song X, Li X, Lu Y, Yang B, Shan H (2016) Knockdown of IncRNA MALAT1 contributes to the suppression of inflammatory responses by up-regulating miR-146a in LPS-induced acute lung injury. Connect Tissue Res 59(6):581–592. https://doi.org/10.1080/03008207.2018.1439480

26. Chen X, Ba Y, Ma L et al (2008) Characterization of microRNAs in serum: a novel class of biomarkers for diagnosis of cancer and other diseases. Cell Res 18(10):997–1006. https://doi.org/10.1038/cr.2008.282
42. Dakhllalah D, Batke K, Wang Y et al (2013) Epigenetic regulation of miR-17 ~ 92 contributes to the pathogenesis of pulmonary fibrosis. Am J Respir Crit Care Med 187(4):397–405. https://doi.org/10.1164/rcrm.201205-0888

43. Hansen TB, Kjems J, Damgaard CK (2013) Circular RNA and miR-7 in Cancer. Can Res 73(18):5609–5613. https://doi.org/10.1158/0008-5472.CAN-13-1568

44. Jeck WR, Sorrentino JA, Wang K, Slevin MK, Burd CE, Liu J, Marzluff WF, Sharpless NE (2013) Circular RNAs are abundant, conserved, and associated with ALU repeats. RNA 19(2):141–157. https://doi.org/10.1261/rna.035667.112

45. Sanger HL, Klotz G, Riesner D, Gross HJ, Kleinschmidt AK (1976) Viroids are single-stranded covalently closed circular RNA molecules existing as highly basepaired rod-like structures. Proc Natl Acad Sci USA 73(11):3852–3856. https://doi.org/10.1073/pnas.73.11.3852

46. Jost I (2018) Development and characterization of circRNA sponges to functionally inhibit miR-122. Dissertation, University of Giessen

47. Memczak S, Jens M, Elefsinioti A et al (2013) Circular RNAs are a large class of animal RNAs with regulatory potency. Nature 495(7441): 333–338. https://doi.org/10.1038/nature12192

48. Burd CE, Jeck WR, Liu Y, Sanoff HK, Wang Z, Sharpless NE (2010) Expression of linear and novel circular forms of an INK4a/ARF-associated noncoding RNA correlates with atherosclerosis risk. PLoS Genet 6(12): e1001233. https://doi.org/10.1371/journal.pgen.1001233

49. Zhong Z, Huang M, Lv M, He Y, Duan C, Zhang L, Chen J (2017) Circular RNA MYLK as a competing endogenous RNA promotes bladder cancer progression through modulating VEGFA/VEGFR2 signaling pathway. Cancer Lett 403: 305317. https://doi.org/10.1016/j.canlet.2017.06.027

50. Fioris G, Zhang L, Follesa P, Sun T (2017) Regulatory role of circular RNAs and neurological disorders. Mol Neurobiol 54(7):5156–5165. https://doi.org/10.1007/s12035-016-0055-4

51. Xu H, Guo S, Li W, Yu P (2015) The circular RNA Cdr1as, via miR-7 and its targets, regulates insulin transcription and secretion in islet cells. Sci Rep 5:12453. https://doi.org/10.1038/srep12453

52. Liu R, Wang Y, Song X, Sun W, Zhang J, Liu Y, Li H, Meng C, Zhang J, Zheng Q, Lv C (2018) Potential regulatory role of circular RNA in idiopathic pulmonary fibrosis. Int J Mol Med 42(6):3256–3268. https://doi.org/10.3892/ijmm.2018.3892

53. Li Z, Huang C, Bao C et al (2015) Exon-intron circular RNAs regulate transcription in the nucleus. Nat Struct Mol Biol 22(2):256–264. https://doi.org/10.1038/nsmb.2959

54. Ashwal-Fluss R, Meyer M, Pamudurti NR, Ivanov A, Bartok O, Hanan M, Evantal N, Memczak S, Rajewsky N, Kadener S (2014) circRNA biogenesis competes with Pre-mRNA splicing. Mol Cell 56(1):55–66. https://doi.org/10.1016/j.molcel.2014.08.019

55. Du WW, Zhang C, Yang W, Yong T, Awan FM, Yang BB (2017) Identifying and characterizing circRNA-protein interaction. Theranostics 7 (17): 4183–4191. https://doi.org/10.7150/thno.21299

56. Wang Y, Wang Z (2015) Efficient backsplicing produces translatable circular mRNAs. RNA 21(2):172–179. https://doi.org/10.1261/rna.048272.114

57. Pamudurti NR, Bartok O, Jens M et al (2017) Translation of Circular RNAs. Mol Cell 66(1):9–21. https://doi.org/10.1016/j.molcel.2017.02.021

58. Hansen TB, Jensen TI, Clausen BH, Bramsen JB, Finsen B, Damgaard CK, Kjems J (2013) Natural RNA circles function as efficient microRNA sponges. Nature 495(7441):384–388. https://doi.org/10.1038/nature12193

59. Liu J, Liu T, Wang X, He A (2017) Circles reshaping the RNA world: from waste to treasure. Mol Cancer 16(1):58. https://doi.org/10.1186/s12943-017-0630-y

60. André PA, Prêle CM, Vierkotten S et al (2015) BARD1 mediates TGFβ signaling in pulmonary fibrosis. Respir Res 16:118. https://doi.org/10.1186/s12931-015-0278-3

61. Link LA, Howley BV, Hussey GS, Howe PH (2016) PCBP1/HRNRP E1 promotes chromosomal integrity by translational regulation of CDC27. Mol Cell Res 14(7):634646. https://doi.org/10.1016/j.molce b.2016.01.0018

62. Aguilar-Martinez E, Chen X, Webber A, Moold A, Seifert A, Hay RT, Sharrocks AD (2015) Screen for multiSUMObinding proteins reveals a multiSIM binding mechanism for recruitment of the transcriptional regulator ZMYM2 to chromatin. Proc Natl Acad Sci USA 112(35):E4854–E4863. https://doi.org/10.1073/pnas.1509716112

63. Yang IV, Pedersen BS, Rabinovich E et al (2014) Relationship of DNA methylation and gene expression in idiopathic pulmonary fibrosis (IPF). Am J Respir Crit Care Med 190(11):12631272. https://doi.org/10.1164/rccm.201408-1452

64. Suaud L, Miller K, Panichelli AE, Randell RL, Marando CM, Rubenstein RC (2011) 4Phenylbutyrate stimulates Hsp70 expression through the Elp2 component of elongator and STAT3 in cystic fibrosis epithelial cells. J Biol Chem 286(52):540835092. https://doi.org/10.1074/jbc.M111.293282

65. Lee JT (2012) Epigenetic regulation by long noncoding RNAs. Science 338:1433–1439

66. Zhao X, Sun J, Chen Y, Su W, Shan H, Li Y, Wang Y, Zheng N, Shan H, Linag H (2018) IncRNA PFAR promotes lung fibroblast activation and fibrosis by targeting miR-138 to regulate the YAP1-twist axis. Mol Ther 26(9):2206–2217. https://doi.org/10.1016/j.ymthe.2018.06.020

67. Zhao X, Sun J, Chen Y, Su W, Shan H, Sun J, Zhang L, Li X, Shan H, Liang H (2018) Inhibition of IncRNA PFRL prevents pulmonary fibrosis by disrupting the miR-26/a/smad2 loop. Am J Physiol Lung Cell Mol Physiol 315(4):LS63–LS75. https://doi.org/10.1152/ajplung.00434.2017

68. Wang X, Cheng Z, Dai LL, Jiang T, Jia L, Jing X, An L, Wang H, Liu M (2019) 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 39(12):e00143–e00119. https://doi.org/10.1128/MCB.00143-19

69. Lu Q, Guo Z, Xie W, Jin W, Zhu D, Chen S, Ren T (2018) The IncRNA H19 mediates pulmonary fibrosis by regulating the miR-196a/COL1A1 axis. Inflammation 41(3):896–903. https://doi.org/10.1007/s12011-017-0753-4

70. Tang Y, He R, An J, Deng P, Huang L, Yang W (2016) The effect of H19-miR-29b interaction on bleomycin-induced mouse model of idiopathic pulmonary fibrosis. Biochem Biophys Res Comm 479(3):417–423. https://doi.org/10.1016/j.bbrc.2016.09.028

71. Savary G, Dewaeles E, Diazzi S et al (2019) The long noncoding RNA DNM3OS is a reservoir of fibromiRs with major functions in lung fibroblast response to TGF-β and pulmonary fibrosis. Am J Respir Crit Care Med 200(2):184–198. https://doi.org/10.1164/rcrm.201807-1237OC

72. Li X, Xu T, Shan H, Jiang H, Sun J, Zhao X, Su W, Yang L, Shan H, Liang H (2018) IncRNA PFAL promotes lung fibrosis through CTGF by competitively binding miR-18a. FASEB J 32(10):5285–5297. https://doi.org/10.1096/fj.201800555R

73. Liu H, Wang B, Zhang J, Zhang S, Wang Y, Zhang J, Lv C, Song X (2017) A novel Inc-PCF promotes the proliferation of TGF-β1-activated epithelial cells by targeting miR-344a-5p to regulate...
map3k11 in pulmonary fibrosis. Cell Death Dis 8(10):e3137. https://doi.org/10.1038/cddis.2017.500

75. Song XD, Cao GH, Jing LL et al (2014) Analyzing the relationship between lncRNA and protein-coding gene and the role of lncRNA as ceRNA in pulmonary fibrosis. J Cell Mol Med 18:991–1003

76. Chen LL, Zhao JC (2014) Functional analysis of long noncoding RNAs in development and disease. Adv Exp Med Biol 825:129–158. https://doi.org/10.1007/978-1-4939-1221-6_4

77. Zheng W (2017) Preliminary study of LncRNA-miRNA-mRNA interaction. Academy of Military Medical Sciences, Chinese People's Liberation Army (In Chinese)

78. Thomas LF, Sætrom P (2014) Circular RNAs are depleted of polymorphisms at microRNA binding sites. Bioinformatics 30(16):2243–2246. https://doi.org/10.1093/bioinformatics/btu257

79. Zhang H, Liu X, Chen S, Wu J, Ye X, Xu L, Chen H, Zhang D, Tan R, Wang Y (2010) Tectorigenin inhibits the in vitro proliferation and enhances miR338 expression of pulmonary fibroblasts in rats with idiopathic pulmonary fibrosis. J Ethnopharmacol 131(1):165–173. https://doi.org/10.1016/j.jep.2010.06.022

80. Wang L, Ma L, Fan H, Yang Z, Li L, Wang H (2016) MicroRNA9 regulates cardiac fibrosis by targeting PDGFRβ in rats. J Physiol Biochem 72(2): 213–223. https://doi.org/10.1007/s13105-016-0471-y

81. Wang YS, Li SH, Guo J, Mihic A, Wu J, Sun L, Davis K, Weisel RD, Li RK (2014) Role of miR145 in cardiac myofibroblast differentiation. J Mol Cell Cardiol 66: 941–955. https://doi.org/10.1016/j.yjmcc.2013.08.007

82. Chen L, Zhang S, Wu J, Cui J, Zhong L, Zeng L, Ge S (2017) circRNA_100290 plays a role in oral cancer by functioning as a sponge of the miR29 family. Oncogene 36(32): 45514561. https://doi.org/10.1038/onc.2017.89

83. Guo JU, Agarwal V, Guo H, Bartel DP (2014) Expanded identification and characterization of mammalian circular RNAs. Genome Biol 15(7): 409. https://doi.org/10.1186/s13059-014-0409-z

84. Li PF, Chen SC, Shao YF et al (2014) The biological function of circular RNA and its role in disease pathogenesis. Acta Biophysica Sinica 30:15–23 (In Chinese)

85. Hentze MW, Preiss T (2013) Circular RNAs: Splicing’s enigma variations. EMBOJ 32(7):923–925. https://doi.org/10.1038/embj.2013.53

86. Jacobs T, Causeret F, Nishimura YV, Terao M, Norman A, Hoshino M, Nikolic M (2007) Localized activation of p21-activated kinase controls neuronal polarity and morphology. J Neurosci 27(32):8604–8615. https://doi.org/10.1523/JNEUR OSCI.0765-07.2007

87. Chacon MR, Navarro AM, Cuesta G, del Pino I, Scott R, Morales M, Rico B (2012) Focal adhesion kinase regulates actin nucleation and neuronal filopodia formation during axonal growth. Development 139(17): 3200–3210. https://doi.org/10.1242/dev.080564

88. Xia X, Han JJ (2018) Systems biology in aging research. Adv Exp Med Biol 1086:1–15. https://doi.org/10.1007/978-981-13-1117-8_1

89. McDonough JE, Ahangari F, Li Q et al (2019) Transcriptional regulatory model of fibrosis progression in the human lung. JCI Insight 4(22): e131597. https://doi.org/10.1172/jci.insight.131597

90. Lorenzo-Salazar JM, Ma SF, Jou J et al (2019) Novel idiopathic pulmonary fibrosis susceptibility variants revealed by deep sequencing. ERJ Open Res 5:00007. https://doi.org/10.1183/23120541.00007-2019

91. Carleo A, Bargagli E, Landi C et al (2016) Comparative proteomic analysis of bronchoalveolar lavage of familial and sporadic cases of idiopathic pulmonary fibrosis. J Breath Res 10(2016):026007. https://doi.org/10.1088/1752-7155/10/2/026007

92. Allen RJ, Guillen-Guio B, Oldham JM et al (2019) Genome-wide association study of susceptibility to idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. https://doi.org/10.1164/rccm.201905-1017

93. Todd JL, Neely ML, Overton R et al (2019) Peripheral blood proteome profiling of idiopathic pulmonary fibrosis biomarkers in the multicentre IPF-PRO registry. Respir Res 20:227. https://doi.org/10.1186/s12931-019-1190-z

94. Kaur A, Mathai SK, Schwartz DA (2017) Genetics in idiopathic pulmonary fibrosis pathogenesis, prognosis, and treatment. Front Med 4:154. https://doi.org/10.3389/fmed.2017.00154

95. Oldham JM, Ma SF, Martinez FI et al (2015) TOLLIP, MUC5B, and the response to N-acetylcysteine among individuals with idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 192(12):1475–1482. https://doi.org/10.1164/rccm.201505-1010

96. Newton CA, Molyneaux PL, Oldham JM (2018) Clinical genetics in interstitial lung disease. Front Med 5:116. https://doi.org/10.3389/fmed.2018.00116

97. Petrovski S, Todd JL, Durheim MT et al (2017) An exome sequencing study to assess the role of rare genetic variation in pulmonary fibrosis. Am J Respir Crit Care Med 196(1):82–93. https://doi.org/10.1164/rccm.201610-2088OC

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