Molecular Biology Reports (2020) 47:3169–3179
https://doi.org/10.1007/s11033-020-05368-9

REVIEW

Decrypting the crosstalk of noncoding RNAs in the progression of IPF

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Received: 30 November 2019 / Accepted: 29 February 2020 / Published online: 16 March 2020

Abstract
Idiopathic pulmonary fibrosis (IPF) is an agnogenic, 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

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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.

lncRNAs 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 lncITPF can increase the expression of its nearby host gene, Itgbl1, through TGF-β1. The expression of lncRNA AP003419.16 and its adjacent gene RPS6KB2, 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].

lncRNAs 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 mRNAs 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 pathopoiesis. 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 ITGBL1, hinders collagen formation, EMT, and myofibroblast mobility in the lung tissues of bleomycininduced 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 mRNAs by at least tenfold [44]. Sanger et al. [45] was the first to discover circRNA, subsequently followed by the

Table 1 The targets and functions miRNAs involved in IPF

miRNAs	Targets	Functions	Quotation
miR-213p	Not clear	Upregulation	[23]
miR-630	Not clear	Downregulation	[23]
miR-29c	Foxo3a	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 ITGBL1	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]

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

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 lncRNA-miRNA interaction network promotes IPF

lncRNAs are not sufficient templates for protein transcription but are involved in epigenetic regulation through miRNAs [65]. lncRNAs probably entangle with miRNAs and influence its expression. In our study, we attempted to ascertain the relationship between lncRNA and miRNA and its function in pulmonary fibrosis. lncRNA can act on miRNA in four ways. Firstly, lncRNAs may act as ceRNA which plays a "molecular sponge" role in miRNA. For example, miR-15a antagonizes the function of lncRNA PFAR, which gives rise to extracellular collagen deposition, fibroblasts proliferation, migration and differentiation. Suggesting that lncRNA PFAR can act as sponge for miR-15a, contributing to fibrogenesis in lung fibroblasts [66]. A similar mechanism occurs between lncRNA NONMMUT065582 and miR-138, and lncRNA NONMMUT022554 and miR-26a, during lung fibrosis [67, 68]. The knock-down of lncRNA 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 lncRNA, DNM3OS (dynamin 3 opposite strand) and its relevant miRNA, display differential expression in experimental or clinical conditions [72]. lncRNA NONMMUT021928, designated as a pulmonary fibrosis-associated lncRNA (PFAL), promotes cell propagation, migration, motility and fibroblast-myofibroblast transition processes by competitively binding to miR-18a [73]. The lnc-PCF accelerates the propagation of epithelial cells through the complementary binding of miR-344a-5p, which has the target gene map3k11 [74]. lncRNA MRAK088388 "sponges" miR-29b-3p to regulate N4bp2, whereas MRAK081523 binds to let-7i-5p to regulate Plxna4 in lung fibrosis [75]. Secondly, some lncRNAs can be generated as precursor molecules of miRNAs. For example, lncRNA H19 can generate miR-675 [76]. Thirdly, lncRNA and miRNA compete for target gene binding, therefore attenuating the inhibitory effect of miRNA on target genes and increasing its stability. Lastly, lncRNA can also regulate the expression levels of miRNA by binding with other proteins.

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

Table 2 The targets and functions of lncRNAs involved in IPF

lncRNA	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	Itgbl1		[12]
AP003419.16	RPS6KB2	Increase the risk of age-associated IPF	[13]
CDKN2B-AS1	CDKN2A	Low expression in IPF predicts lung cancer	[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 pathophysiological 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_102101 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 plateletderived 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

Table 3 The targets and functions of circRNAs involved in IPF

circRNAs	Targets	Functions	Quotation
circRNA_100906	miR3245p/3305p	Downregulation in IPF	[73]
circRNA_102101/102100	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]

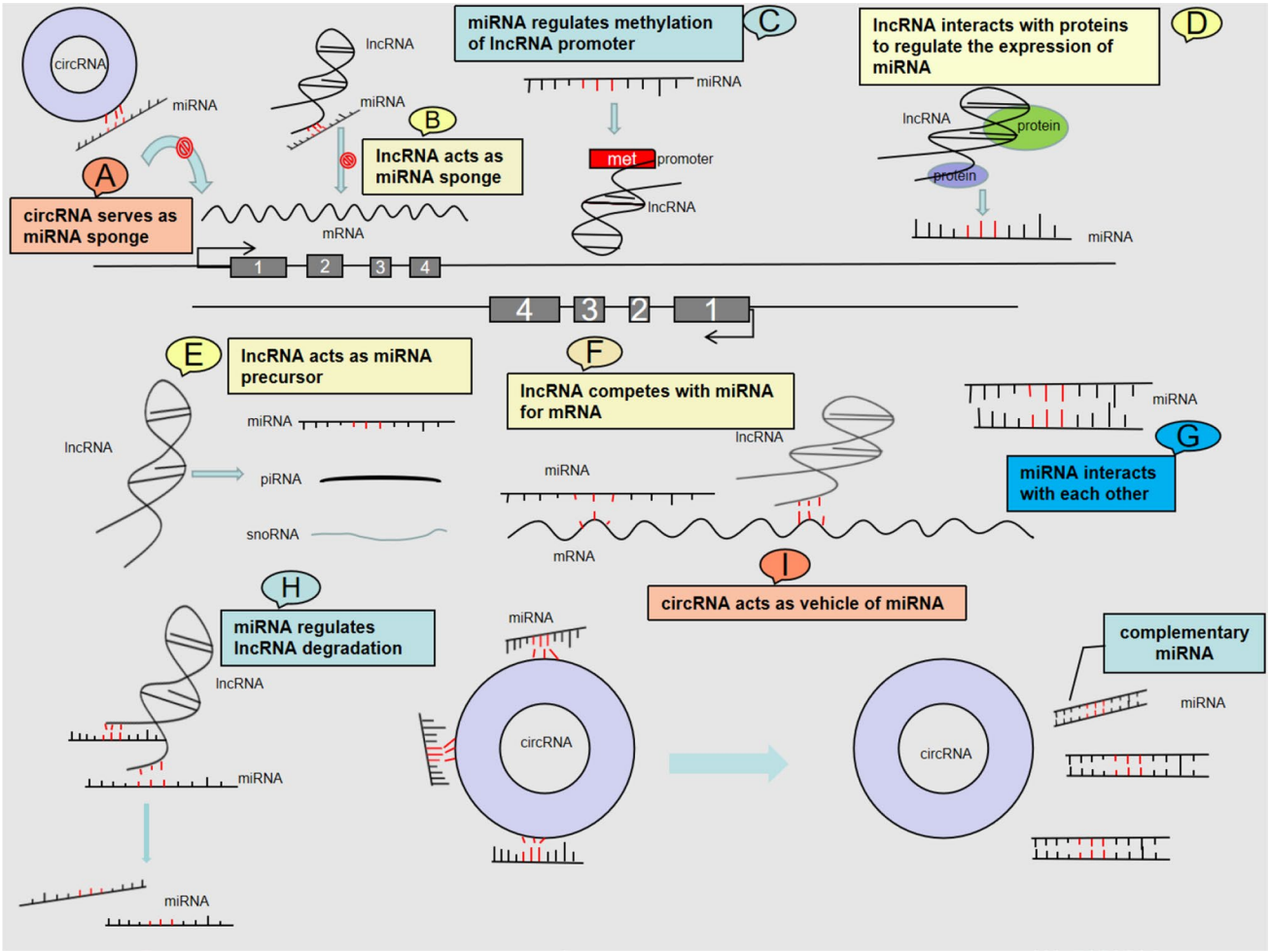

Fig. 1 The crosstalk among ncRNAs. **A** circRNAs act as miRNAs sponges to repress target genes. **B** lncRNAs sponge miRNAs to regulate the expression process of target genes. **C** miRNAs regulate the expression of lncRNAs by regulating the methylation of lncRNAs promoters. **D** lncRNAs can also regulate the expression levels of miRNAs through other proteins. **E** Some lncRNAs can be generated as precursor molecules of miRNAs and others, like piRNAs, snoRNAs, etc. **F** lncRNAs and miRNAs compete for binding opportunities to target genes. **G** miRNAs can regulate each other through complementarily binding.**H** miRNAs accelerate the degradation of lncRNAs. **I** circRNAs function as miRNAs transporters, possibly even releasing their cargo by cleavage through a perfectly complementary miRNA

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 lncRNA, 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

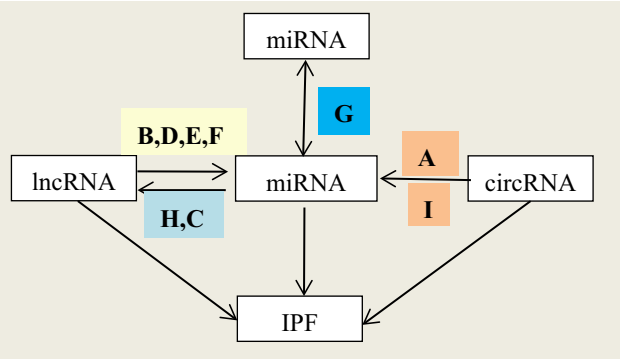

Fig. 2 The roles of lncRNA, miRNA, circRNA, and interplay among ncRNAs in the development of IPF. ncRNAs include lncRNAs, miRNAs and circRNAs, each of which drive the progression of IPF. Additionally, lncRNAs can interact with miRNAs in B, D, E and F (yellow textbox as described Fig. 1) ways, thereby influencing the target mRNA's expression in IPF. In turn, miRNAs can react to lncRNAs in C and H (green textbox as described Fig. 1) ways. circRNAs sufficiently act on miRNAs in A and I (orange textbox as described Fig. 1) ways, influencing the pathogenesis of IPF. Some studies have revealed that miRNAs could interact with each other through G (blue textbox as described Fig. 1) in the pathogenesis of lung fibrosis

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 lncRNAs, 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.

Acknowledgements This study was funded by Department of Science and Technology of Jilin Province (Grant No. 20190201279JC); and The Provincial Special Fund for Industrial Innovation from Jilin Province (Grant No. 2017C058-3). Thanks also for the editorial work of Editage Ltd.

Compliance with ethical standards

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

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