Non-Coding RNA in Idiopathic Interstitial Pneumonia and Covid-19 Pulmonary Fibrosis

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Abstract

Pulmonary fibrosis is the major manifestation of idiopathic interstitial pneumonia as well as post-COVID-19 complications. The pathogenesis of PF is a complex molecular process that involves many types of cells, proteins, genes, and regulatory elements. The non-coding RNA is the main regulatory element in this process which mainly includes; miRNA, circRNA, and lncRNA. These regulatory elements control the expression of many important genes and various pathways that are involved in the pathogenesis of pulmonary fibrosis. Identification and molecular mechanisms by which these non-coding RNA molecules works are very important because they do not only help to understand the molecular basis of the disease but could also serve as a potential diagnostic/prognostic marker as well as therapeutic targets. In this review, we have provided the latest findings and discussed the role of these regulatory elements in various biological processes and pathways involved in the pathogenesis of pulmonary fibrosis associated with IIPs and Covid-19.

Introduction

Pulmonary fibrosis is a result of myriad of conditions including autoimmunity, exposure to drug or environmental antigens, infections; in a large group of patients, the etiology is not known and the entity is labelled as idiopathic interstitial pneumonitis (IIP) [1]. Idiopathic pulmonary fibrosis (IPF) and non-specific interstitial pneumonia (NSIP) are classical example of IIP. Pulmonary fibrosis, due to both IPF and NSIP, is a relentlessly progressive that can lead to respiratory failure and untimely death. Unfortunately, the current therapeutic options, at the best, are only able to marginally slow-down the progression of the IIPs. Recently, Covid-19 has also led to addition of large number of patients with post-infectious lung changes. Although, in a large number of patients the changes are reversible with time; still, this pandemic has led to the surge in the cases of pulmonary fibrosis as a sequela to COVID-19 [2] [3]. The treatment of post-Covid pulmonary fibrosis is yet not known.

Pulmonary fibrosis occurs as a result of interplay of multiple complex processes (Fig. 1) that includes lung injury, abnormal tissue repair, fibro-proliferation, and extracellular matrix depositions [4]. Various pathways involved in the pathogenesis of pulmonary fibrosis includes apoptosis, inflammation, coagulation, angiogenesis, and proteolytic/anti-proteolytic balance [5]. Many of these pathways are regulated by the change in the expression of various protein coding genes that play a vital role in the pathogenesis of the disease. These genes are further regulated by different classes of non-coding RNAs.

Non-coding RNA (ncRNA) does not code for protein, nevertheless, it does not mean that these entities are redundant. Majority of the human genomes are transcribed into ncRNAs. These ncRNAs control diverse levels of gene expression in various biological processes in development and physiology, including, transcription, chromatin remodeling, RNA editing, splicing as well as translation and turnover [6]. Few functionally important ncRNAs are - long non-coding RNA (lncRNA), circular RNA (cirRNA), and small nucleolar RNAs (snoRNAs). It has been reported that genetic and epigenetic defects in miRNA and their processing machinery are common trademark of many cancers in human. Similarly, other ncRNAs, such

as long non-coding RNA (lncRNA), circular RNA (cirRNA), small nucleolar RNAs (snoRNAs) also contribute to the progression of multiple human disorders [7].

Recently, several studies have demonstrated the connotation of non-coding RNAs in various pulmonary diseases and their critical functions in lung development and homeostasis, widening a new paradigm in the diagnosis, control, and treatment of pulmonary diseases [8]. The current article provides a comprehensive review of the role of ncRNAs in pathogenesis of pulmonary fibrosis in IIPs and Covid/post-covid pulmonary fibrosis.

Classes Of Non-coding Rna

Broadly, ncRNAs can be categorized by the length, as short or small non-coding RNAs with a length of shorter than 200 nucleotides and long non-coding RNA with a length of more than 200 nucleotides. Another way of classification is based on functionality with housekeeping ncRNAs such as ribosomal RNAs (rRNAs) and transfer RNA (tRNA), or regulatory ncRNAs such as micro RNAs (miRNAs), small nuclear RNAs (snRNAs), piwi-interacting RNAs (piRNAs), tRNA derived small RNAs (tsRNAs) and long noncoding RNAs (lncRNAs) [9]. There is another class of ncRNAs called circular RNAs, consisting of a covalently closed continuous loop lacking both 5' cap and 3' tail [10]. Figure 2 summarized the three main non-coding RNA and their biogenesis.

Microrna

miRNAs, ~ 20 nucleotides long and single stranded ncRNAs, are expressed endogenously and regulates the gene expression at post transcriptional level. Genes that encode miRNAs are ubiquitously present in the genome. Partly, miRNAs are encoded inside or overlap to 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 [11]. During the biogenesis of the miRNA, it passes through multiple process such as transcription, nuclear maturation, exportation followed by cytoplasmic processing before evolving into a functional entity [9].

Lncrna

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 [9]. In last the decade, as a result of advancement in the high-throughput sequencing and computational analysis, lncRNA has become a hotspot in scientific research. lncRNA biogenesis takes place in the nucleus and express in tissue specific manner [12]. 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, posttranscriptional modification is characterized by 5' capping and 3' polyadenylation [9].

Circrna

Circular RNA (CircRNAs) are non-coding transcripts that originate due to back-splicing mechanism which results in joined head-to-tail splice site forming covalently linked circular RNA molecule. The size of circRNA can vary from100 nucleotides to over 4 kb and harbour single or multiple exons [13], [14]. They are highly stable due to lack of ends and are highly tissue/cell specific in nature [14] [8]. The biogenesis of circRNA occurs as a result of splicing events followed by circularization of introns or exons [16].

Pulmonary Fibrosis And Non-coding Rna

Pulmonary fibrosis is a complex process that involves both coding and noncoding genes and transcripts, a recent study on coding and non-coding RNA implies the intricate network of mRNA/LncRNA/miRNA/CircRNA in the pathogenesis of pulmonary fibrosis [17]. The most widely studied pulmonary fibrosis associated disease is IPF, because it is more prevalent and has high morbidity and mortality rate. Even after decades of study on the pathogenesis of the IPF, the exact etiology of this disease is still not well-defined. In the following sections we have discussed the role of three main ncRNA in pulmonary fibrosis.

1. Mirna

In the last decade, there has been a rapid increase in the studies exploring the role of non-coding RNA in pulmonary fibrosis. 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 on miRNA in pulmonary fibrosis was done by Caedens et al., they found the overexpression of miR-199a-5p in the lungs of IPF patients and bleomycin induced mouse models; it was found that miR-199a-5p activates the fibroblasts by targeting CAV-1 and through modulation of TGF-β signaling [18]. 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 [19]. Study by pandit et al., showed that out of 450 miRNAs, around 10% of the miRNAs are dysregulated in IPF patients [20]. 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 HMGA1, confirming profibrotic effects.

Study by 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 [21]. miR-21 is also involved in nanoparticles mediated lung injury and fibrosis. In animal model, knocking out this miRNA ameliorates the lung injury and inflammation [22]. Another important miRNA is miR-22, in-vivo study on BLM-induced mice showed increased expression of miR-22. In-vitro experiments suggests 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 [23].

In macrophages of IPF and BLM induced mice, the overexpression of miR-142-5p and downregulation of miR-130a-3p has been observed. Inhibition of miR-142-5p and upregulation of miR-130a-3p reduces the fibrosis burden via STAT6 pathway that targets the peroxisome prolifilator-activated receptor γ (PPARγ) a STAT6 coordinator and inhibitor of cytokine signaling 1 (SOCS1) respectively. It facilitates the activation of macrophage and contribute to widespread tissue fibrosis [24].

In A549 cell line and BLM mouse miR-26a is under-expressed, and its upregulation reduces the EMT transition (epithelial-mesenchymal transition) via targeting HMGA2 (high mobility group AT-hook 2) [25]. 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 [26]. SMAD2, which is a key mediator of lung fibrosis and is associated with TGF-β1 signaling pathway and it can be targeted with miR-486-5p as shown by Ji et al., in mouse model. miR-486-5p is upregulated in IPF patient's lung tissues as well as in BLM-induced mouse models [27].

In another study of ILD patients which included two cohorts of Hypersensitivity Pneumonitis and NSIP patients, miRNA profiling of serum samples reveals a difference in the miRNA's expression of the two distinct 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 [28].

Pulmonary fibrosis is another major implication of post covid pulmonary fibrosis [29]. miRNAs are also vital in COVID-19 associated implications including pulmonary fibrosis [29]. Lung is the primary organ affected by the SARS-CoV-2 infection. Many miRNAs have been identified as the potential therapeutic target in COVID-19 such as miR-17-5p which has been reported to play a key role as an anti-viral molecule in pulmonary infections [30]. miR-574–5p is an important negative regulator of pro-inflammatory response that inhibits TLR4/ NF-kB signaling and attenuates acute respiratory distress syndrome (ARDS) [31]. ARDS is also characterized by the presence of inflammation and a subset of patients also develops fibrosis [32].

Apart from above mentioned miRNAs, there are many other miRNAs which play important role in pulmonary fibrosis. For example, miR-17 ~ 92 cluster and miR-200 family which has 6 and 5 species of miRNA, respectively, have been involved in regulation of cellular senescence in pulmonary fibrosis [33].

The miRNAs implicated in IIPs and post Covid fibrosis and different biological processes, and pathways regulated by these are summarized in the Table 1.

Table 1

miRNA	Expression	Target	Function	Biospecimen origin	Reference
miR-199a-5p	Up	CAV1	Activation of Lung Fibroblast through TGF-β	lung tissue of IPF patients, BLM-mouse	[34]
miR-26a	Down	HMGA2	Induces Epithelial to mesenchymal transition	BLM-mouse, A549 cells	[35]
miR-9-5p	Up	TGFBR2	Inhibits pro-fibrogenic transformation of fibroblasts and prevent organ fibrosis	BLM mouse, IPF lung	[36]
miR-130a-3p	Down	PPARγ	regulation of profibrotic gene in macrophages	BLM-mouse, IPF patient's macrophage	[37]
miR-21	Up	ADAMTS-1	Increases Col1 and Col3 and promotes lung fibrosis	PB of IPF patients and BLM-Rat	[38]
miR-185, miR-186	Down	COL5A1	EMT transition and Collagen V	IPF lung, A549 and HCC827 cells	[39]
miR-1307-3p	High	3' UTR of SARS-CoV-2, BCL2, PI3K	Suppression of endocytosis, exocytosis, proliferative, and diabetes signaling pathways	Lung tissue	[40]
miR-29c	Down	Fas	Cessation of Fas mediated apoptosis	lung fibroblast, IPF lungs	[41]
miR-34a	Up	SIRT1	Cellular senescence inhibition	Alveolar epithelial cell and lung fibroblast	[42]
miR-155	Up	SHIP-1, liver X receptor, Mep1a	EMT transition, collagen synthesis	HU-VEC, NR8383 murine monocytes/macrophage cells, Mouse primary lung endothelial cells	[43]–[45]
miR-199	Up	Caveolin-1	Promotes proliferation & differentiation	Mouse Model, MR-5, hFL1, A549, HEK-293	[46], [47]
miR-328	Up	FAM13A	Promotes proliferation and increases the expression of PF markers	Rat-model, Macrophages, Lung fibroblasts	[48]

miRNA	Expression	Target	Function	Biospecimen origin	Reference
Let-7	Down	LOX1 HMGA2	Reduces cell damage	Mouse MLE-12, A549, RLE-6TN Human lung samples	[49]
MiR-193	Down	SHH	Increases autophagy and inhibits fibrinogen expression	Mouse, A549	[50]
MiR-708	Down	ADAM17	Inhibits cell differentiation	Mouse A549, MRC-5 Human Lung Samples	[51]

Table 2

circRNA	Expression	Target	Function	Biospecimen	Reference
circ_406961	Low	ILF2	Inhibitory effects on inflammation	PM2.5 treated BEAS-2B cells	[67]
circZC3H4	High	ZC3H4 protein via miR-212	Macrophage activation, fibroblasts proliferation and migration	Alveolar macrophage of silicosis patients	[57]
circHECTD1	Low	ZC3H12A	M1/M2 polarization, inflammation initiation	Alveolar macrophage of silicosis patients	[58]
circHIPK2	High	miR-506-3p	induce sigma-1 receptor-associated endoplasmic reticulum stress	Lung fibroblast	[60]
circ-012091	Low	PPP1R13B	Proliferation and migration of via ERS and autophagy pathway	Lung fibroblast	[61], [62]
LncRNA					
MEG3	Up	TAT3, TP63, KRT14, YAP1	Enhances cell migration, tissue remodeling	IPF lung tissue	[68]
MALAT1	Down	Hexokinases	Aberrant macrophage activation	IL-4 treated macrophage	[69]
NEAT1	Down	Rbm7, BRCA1	Triggering of apoptosis	Rbm7-deficient mouse, bleomycin-induced fibrosis mouse, nonhematopoietic (CD45-) cells and RBM7−/− HEK293 cells	[70]
ITPF	Up	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	[71]

circRNA	Expression	Target	Function	Biospecimen	Reference
lncTERRA	Up	Genes & component associated with telomeres and mitochondria	Regulates telomeric and mitochondrial functions	Blood from IPF patients, BLM-mouse, A549, MLE-12	[72]
lncR-PCF	Up	mir-344a-5p	Promotes pulmonary fibrogenesis	IPF lungs, BLM-mouse, RLE-6TN cells	[21]
SIRT-AS	Up	miR-34a	SIRT1-AS overexpression inhibited TGF-β-mediated EMT	BLM-mouse lung	[73]
ZEB1-AS1	Up	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	[74]
HOTAIRM1	Down	IL-17 signaling pathway	Regulates viral transcription and inflammatory development	Bronchoalveolar lavage fluid of COVID-19 patients	[75]
DANCR	Down	REL, RELA, and NFkB1 and to AChE and IL-1b	Promoted infection	Inflammatory prone lung tissue	[76]
MALAT1, NEAT1	Up	CAPN1	Inflammatory response	BALF, NHBE Cells	[77]–[80]

2. Circular Rnas

Advancement in the computational tools in OMICS technology led to the identification of novel transcripts including circular RNA. 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 a recent study, RNA sequencing led to the identification of 74 differentially expressed circRNAs in BLM-induced pulmonary fibrosis in mice [52]. In the same study, the investigators showed that circRNAs work by interacting with other non-coding RNAs to regulate pulmonary fibrosis via different regulatory mechanisms. They showed that circ949 and circ057 create a network with lnc556 and lnc865 and

simultaneously regulate miR-29b-2-5p by targeting STAT3 phosphorylation [52]. Another study by Li et al., led to the identification of 67 dysregulated circRNAs in the serum sample of IPF patients. Among them a total of 38 transcripts were overexpressed, while 29 were downregulated. 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 and others functioned as pulmonary fibrosis biomarker [53].

Many circRNA works by interacting with miRNA, such as circRNA_010567 which has a profibrotic function. Its function is partly mediated by miR-141/TGF- β1 [54]. TADA2A is a circRNA which 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 [55].

In SiO2 mediated pulmonary fibrosis (silicosis) that involves the alveolar macrophages, the SiO2 particles stimulates different factors at the inflammatory sites which also includes ncRNA [56]. 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 silicosis patients. The protein expression of ZC3H4 is regulated by circZC3H4 via miR-122, which further activates the alveolar macrophages, these activated macrophages lead to the fibroblast proliferation and migration [57]. 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 interestingly found to be accumulated in the lung tissues. Evidence suggests that circHECTD1 can competitively inhibits ZC3H12A ubiquitination with HECTD1 for ZCH3A12A protein and affects the macrophage polarization and activation, and suppresses inflammation cascade [58]. Moreover, higher expression of circHECTD1 is also involved in the transition of endothelial and epithelial cells into mesenchymal cells [59]. 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 [60].

Another study, showed that PPP1R13B gene derived circ-012091 was downregulated and negatively regulates the expression of PPP1R13B protein in the lung fibroblasts [61]. 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 [61], [62].

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 [63].

CDR1as functions as a miRNA sponge and is associated with miR-7, this miRNA is thought 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 [64].

As evident, acute lung injury can also lead to pulmonary fibrosis as a result of infection or any physical or chemical trauma [65]. In rat model, Ye et al., find 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 [66].

3. Lncrna

Another major class of non-coding RNA is lncRNA which are more than 200 nucleotides in length and is the second most widely studied ncRNA in human diseases after miRNA. Multiple studies have shown the dysregulation of lncRNA in fibrotic diseases, including pulmonary fibrosis as well as in acute lung injury [81], [82].

Epithelial cells are considered to be the initial site for microinjuries which leads to alteration in the cellular microenvironment, ECM deposition, and fibroblast activation [83], [84]. Using single-cell RNA-sequencing, Goket et al., identified the 21 differentially expressed lncRNAs in the epithelial cells, lncMEG3 was the most significant. Previous studies have shown that lncMEG3 influences the differentiation of epithelial cells and increases their migration by regulating multiple genes, which include STAT3, KRT14, TP63, YAP1, TGF-β and others [85].

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 secrets chemokines which lead to the recruitment of atypical monocytes in the cellular microenvironment which drives pulmonary fibrosis [86]. 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 [87].

lncAP003419.16 is highly expressed in IPF patients and TGFβ1-treated epithelial cells [88]. lncAP003419.16 drives pulmonary fibrosis by targeting RPS6KB2 dependent mTOR signaling pathway [89]. 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 [90]. 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, however, they do not share the same promoter, ITPF promoter is bounds 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). Analysis also revealed that ITPF is correlated with clinicopathological characteristics of IPF patients [90].

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; like lncITBP, it also promotes the lung fibrosis by increasing the proliferation and migration of fibroblasts. Inhibition of lnc949 in vivo and in vitro can suppress the progression of fibrogenesis, indicating its role as a potential therapeutic target in pulmonary fibrosis [91].

MALAT1 is a prominent lncRNA involved in many diseases including acute lung injury [82]. 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 [92]. P65, a subunit of NF-kB can bind to the promoter of MALAT1, suggesting it as a direct target of LPS-induced activation of NF-kB, which increases pro-inflammatory cytokines IL-6, IL-12, and TNF- α in LPS-induced macrophages dependent on CLec16a gene. 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. Hence, MALAT1 controls pulmonary fibrosis by triggering activation of macrophages [92].

In silicotic rat lung, upregulated lncRNA LOC103691771 was found to be associated with macrophage activation and fibroblast differentiation through TGFβ1-Smad2/3 signaling pathway [93].

A recent study by Ma et al., on the lung tissue exposed to PM2.5 revealed a total of 309 differentially expressed lncRNA, 201 upregulated and 108 downregulated. PM2.5 have been reported in EMT transition which contributes in lung fibrosis. Among these upregulated lncRNA, it was discovered that Gm16410 regulates the TGF-β1/Smad3/p-Smad3 signaling pathway [94].

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 siRNA that mimics the miRNAs targeting the SARS-CoV-2 to inhibit fatal lung fibrosis. Among those 13 siRNAs, 27/RdRP targets the nsp12 region of the SARS-CoV-2 virus, functions similar to miR-27, and inhibits TGF-β-induced pulmonary fibrosis and

COL1A1 in human lung cells. Thus, implying the role of siRNA as a potential therapeutic target in COVID-19 associated pulmonary fibrosis [95].

Conclusion

Currently, we have limited knowledge of molecular pathogenesis of pulmonary fibrosis in IIPs and COVID 19; and also, there are limited therapeutic options. In last few decades, ncRNAs emerges as a key regulator in multiple human diseases, including pulmonary fibrosis. These non-coding transcripts are involved in several pathophysiological processes such as inflammation, apoptosis, multiple cell signalling pathways involved in the genesis of fibrosis. Additionally, experiments involving cell lines and mouse models have demonstrated that many of these ncRNA as potential therapeutic targets. Therefore, future research, including interventional studies, must focus on ncRNAs to find detailed molecular processes involved in the pathogenesis of pulmonary fibrosis and newer therapeutic targets.

Declarations

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Author Contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by MSA, JS and Md. Tanjim Alam and Vijay Hadda. The first draft of the manuscript was written by Mohammad Shadab Ali and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Compliance with Ethical Standards

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

Conflict of Interest

None

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Figures

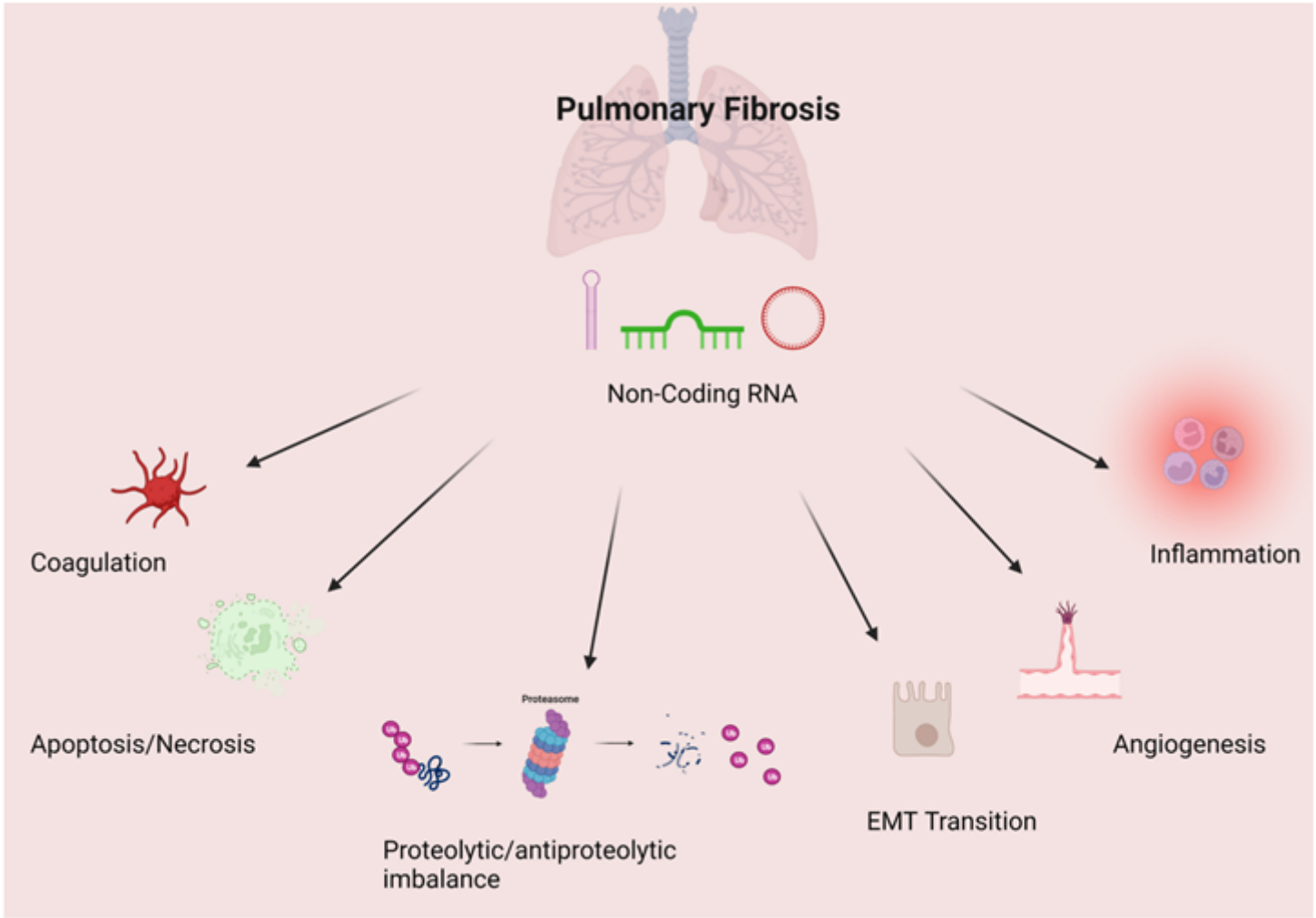

Figure 1

Non-Coding RNA involve in the major biological processes in Pulmonary Fibrosis

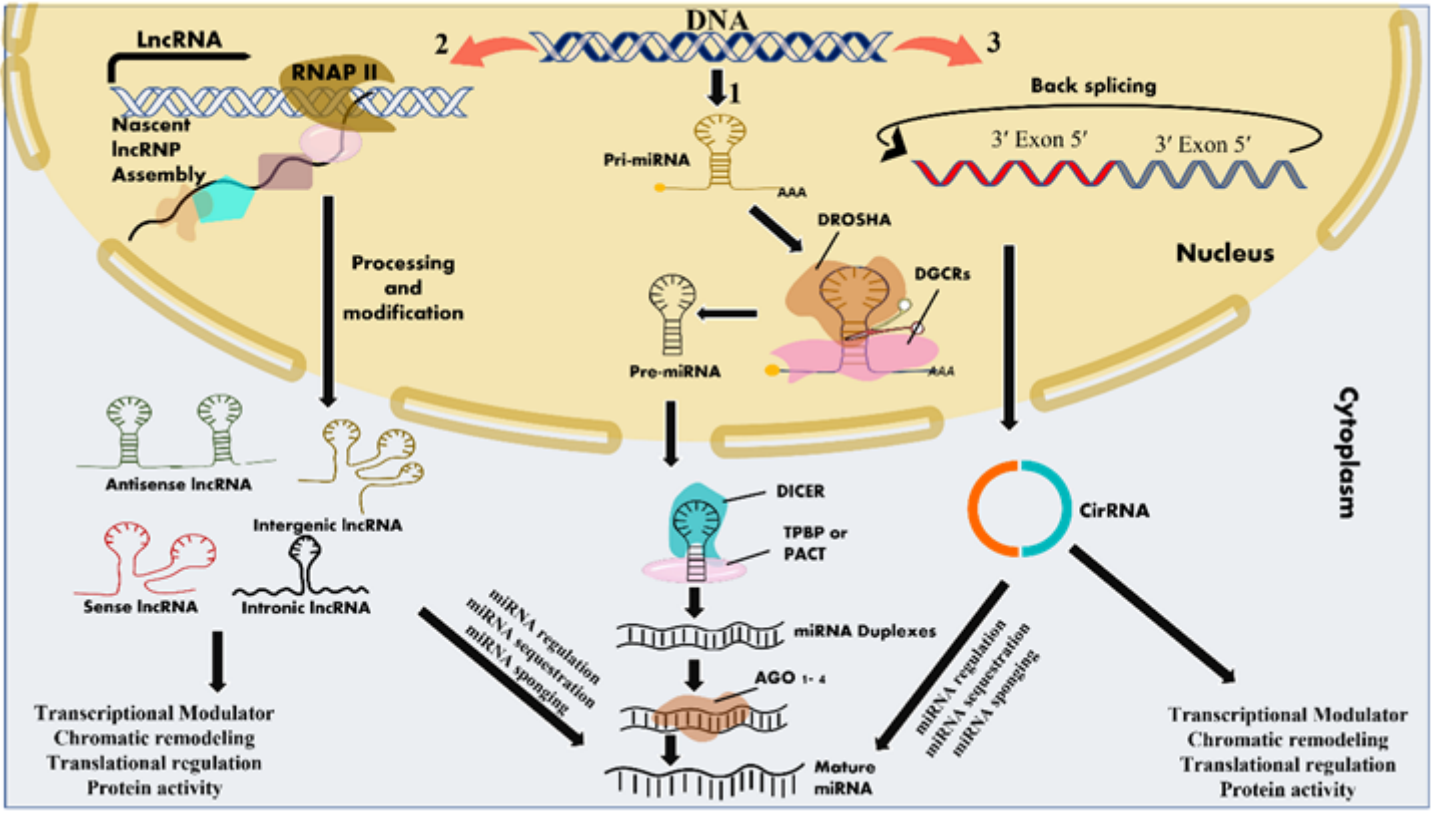

Figure 2

Biogenesis and Major functions of ncRNAs