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Review Article

THE TRANSLATIONAL POSSIBILITY OF TARGETING LncRNAs AS A THERAPEUTIC STRATEGY FOR IDIOPATHIC PULMONARY FIBROSIS

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ABSTRACT

Idiopathic pulmonary fibrosis (IPF) is an interstitial lung disease (ILD). IPF causes stiffness in the lungs which makes it difficult to breathe and get oxygen to the bloodstream. IPF is a particularly severe form of lung fibrosis with no completely known etiology and a median survival of 2.5–3.5 years after diagnosis. The phenotypic changes in the lung fibroblasts are believed to contribute to the development of idiopathic pulmonary fibrosis. Long intergenic non-coding RNAs (LncRNAs) have been identified as novel regulators of gene expression and protein activity. In non-stimulated cells, it showed reduced proliferation and inflammation but no difference in the fibrotic response of IPF fibroblasts. These functional changes in non-stimulated cells were associated with changes in the expression of the histone marks, H3K4me1, H3K4me3, and H3K27ac indicating a possible involvement of epigenetics. Following activation with TGF-β1 and IL-1β, it demonstrated an increased fibrotic but reduced inflammatory response in IPF fibroblasts. No significant difference in proliferation following PDGF exposure was observed. The LncRNAs, LINC00960, and LINC01140 were upregulated in IPF fibroblasts. Knockdown studies showed that LINC00960 and LINC01140 were positive regulators of proliferation in both control and IPF fibroblasts but had no effect on the fibrotic response. Knockdown of LINC01140 but not LINC00960 increased the inflammatory response, which was greater in IPF compared to control fibroblasts. Overall, this review study tries to emphasize the role of LncRNAs as regulators of proliferation and inflammation in human lung fibroblast, a biomarker in IPF, and a novel treatment approach.

Keywords: Pulmonary fibrosis, LncRNAs, Idiopathic Lungs disease.

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INTRODUCTION

Pulmonary fibrosis can be also called as interstitial lung disease (ILD). ILD is a group conditions that result in inflammation and formation of scars around the alveoli. The process of scarring of the lungs is called fibrosis. Fibrosis converts the normal tissues in the lungs to get thicker and stiffer. Scarring of lungs makes it hard to function the gaseous exchange. PF can be the outcome of particular disease conditions, medication, and genetics. Most often the cause is unknown. This overall cascade is called idiopathic pulmonary fibrosis (IPF) [1-4].

Interstitial lung disease (ILD) is parental terminology used for a group of diseases that result scarring (fibrosis) of the lungs. The scarring of normal tissue leads to stiffness in the lungs which makes it difficult for respiration and get oxygen to the bloodstream. Lung damage from ILDs in most of the time is irreversible, irreparable, and gets worse over time [2,5,6].

The ATS/ERS classification defines IPF as "a specific form of chronic fibrosing interstitial pneumonia of unknown etiology, localized to the lung, and associated with the histological entity of usual interstitial pneumonia" [7,8].

PF enhances the cause of morbidity and mortality globally with very less known therapeutic as well as treatment options. IPF is a severe type of pulmonary fibrosis with mostly unknown etiology and an average survival of 2.5–3.5 years after diagnosis. The prevalence of pulmonary fibrosis is gradually increases about 0.2% of worldwide, geriatric peoples are affected as compared with adult [9,10]. Once this disease was thought to be a chronic inflammatory process, but growing evidence suggested that the fibrotic activity in IPF is regulated by abnormally activated alveolar epithelial cells (AECs). This infection is symbolized by the accelerated and uncontrolled activation of epithelial cells, which releases variety of mediators resulting in the enlargement, elongation, and metastasis as well as increment of the fibroblast/myofibroblast population with the simultaneous aberrant accumulation of extracellular matrix and the destruction of the lung morphology. TGF-β activates fibroblasts for overexpression of fibrotic matrix proteins which increase the production of profibrotic cytokines into the alveolar epithelial cells. IPF is one of the most ever forms of idiopathic interstitial cases of pneumonia with increasing prevalence over the time period. Confirm diagnosis depends on the presence of the so-called usual interstitial pneumonia (UIP) pattern on high-resolution computed tomography and/or on surgical lung biopsy [2,11-13].

PROGNOSIS, EPIDEMIOLOGY, AND TYPES

Multiple detectable diseases and pathological conditions can result in scarring of the lungs, but a large number of PF cases are caused by unknown reasons and are diagnosed as idiopathic pulmonary fibrosis (IPF). The point at which the diseased state translates into idiopathic is unknown as the majority of the cases of pulmonary fibrosis are the result of factors that cannot be confirmed which makes treatment more complicated and hard [14]. IPF remains a very serious condition with patient mortality of 3–5 years after the diagnosis. The primary complications are respiratory failure along with pulmonary hypertension, heart failure, pneumonia, and lung cancer. IPF is a rare disease with an occurrence of 13–20 individuals per every 100,000 people globally diagnosed with the disease [15]. In few cases, the pattern of pulmonary fibrosis is seen in families which suggest the genetic role in the diagnosis of the cases of IPF. This type of case is called familial pulmonary fibrosis. Up to date, only 100 such families have been confirmed for genetically passing this disease globally [15,16]. The mortality rate of IPF is higher in males, the previous study was done by Olson *et al*. reported that from 1992 to 2003 in USA, 28.4% male peoples are died which increases the mortality rate 41.3% during this study time frame [17,18].

IPF is categorized based on pulmonary function tests are mild, moderate, severe, and very severe. It can further be categorized as idiopathic non-specific interstitial pneumonia (NSIP), cryptogenic organizing pneumonia (COP), and sarcoidosis [11,19]. High-resolution CT in a 73-year-old patient with IPPF. CT shows changes consistent with the usual interstitial pneumonia pattern, characterized by reticular opacities, traction bronchiectasis, small ground glass opacifications,

and honeycombing manifested as sub-plural clustered cystic airspaces with well-defined walls (Fig. 1).

PATHOGENESIS OF IPF

The pathogenesis of IPF is generally characterized in three stages: (1) Genetic mutation, environmental contaminants and aging that induced pulmonary fibrosis, (2) activation of TGF-β and unfold protein response (UPR), epithelial to mesenchymal transition, and fibrocyte recruitment, and (3) fibroblast differentiation, matrix deposition, and remodeling (10). Pulmonary fibrosis is the terminal stage which is characterized by excessive matrix formation leading to destruction of normal lung structure and finally succumbing to death. Histologically the lugs with IPF have varying regions of normal lung parenchyma, interstitial inflammation, fibrosis, and honeycombing [2,20]. The pathophysiological bases of IPF have been the matter of much debate over the past few decades. The growing number of evidence suggests that IPF represents a separate disorder which is the result of fibrogenesis in part or in multifocal lungs epithelial microinjury. The growing stress over the AEC (Alveolar Epithelial Cells) leads to cell death resulting in distorted fibroblastic interactions and disordered repair process resulting in fibrosis [21] (Fig. 2).

INITIATION OF FIBROSIS: FACTORS AND CAUSATIVE AGENTS

The factors and causative agents responsible for the initiation of fibrotic process in lungs remain largely undefined. It is generally accepted that the consecutive chronic lungs injury is caused by genetic predisposing factors and injurious environmental agents [21,22]. Although IPF is a sporadic disease, familial occurrence exists. The familial clustering of adult idiopathic interstitial pneumonias (IIP) shows that genetic factors might play a leading role in disease development [23,24], with the growing number of evidence, it is believed that IPF results from the association of genetic predisposition to epithelial cell dysregulation with environmental factors, leading to the "multiple hit hypothesis" [23,24]. Viral infection has been promulgated as initiators of fibrotic cascade. Viruses involved in the pathogenesis of IPF include Epstein-Barr virus (EBV), human herpes virus 7 and 8, cytomegalovirus, hepatitis C virus, herpes simplex virus, parvovirus B19, and torque teno virus [23,25]. After 1970s, inter-relation between gastroesophageal reflux and hiatal herniation and IPF has been recognized. In IPF, the prevalence of GERD is estimated to be up to 90%. Emerging evidence suggests the involvement of chronic microaspiration due to the subclinical aspiration of small droplets for which GERD is a risk factor. GERD and silent microaspiration are inter-related with several lung diseases including post-transplantation rejection [26-28].

IMMUNE MOLECULES INVOLVED

It is generally accepted that the pulmonary fibrosis is caused by consecutive chronic subclinical lungs injury leading to epithelial damage and subsequent destruction of the alveolar-capillary membrane due

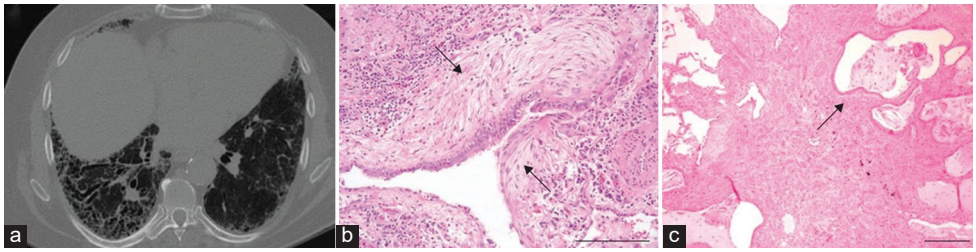

Fig. 1: Consistent changes with the usual interstitial pneumonia pattern with sub-plural clustered cystic airspaces with well-defined walls (a) Histopathological features of usual interstitial pneumonia, (b) dense fibrosis and honeycomb lesion

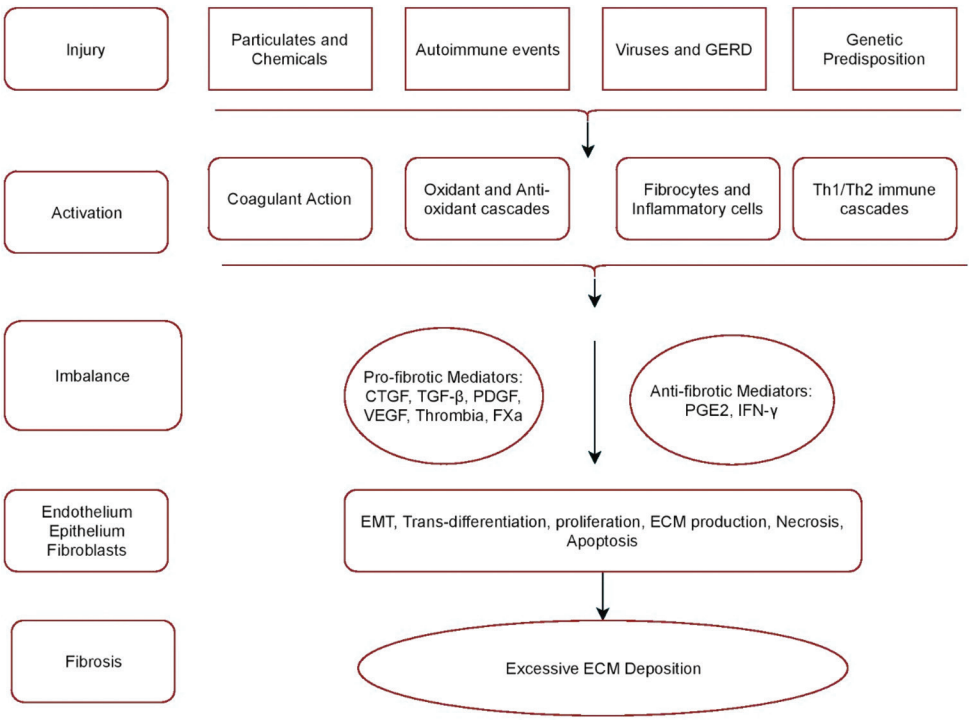

Fig. 2: Pathogenesis of IPF

to various underlying injury mechanisms. Repairing and rejuvenating damaged tissues are a normal homeostatic mechanism of body that complies the clearance of dead or damaged cells after injury and the maintenance of tissue integrity [29,30]. The destructed alveolar capillary membrane leads to activation of coagulation pathway, oxidant and anti-oxidant pathway, and mobilization of inflammatory cells as well as Th1/Th2 cells which initiates the formation of fibroblasts and myofibroblasts in the extracellular matrix of alveoli (Fig. 3). The histopathological study of ECM of alveoli shows the presence of various pre-fibrotic, fibrotic, pro-fibrotic, and anti-fibrotic mediators [31,32].

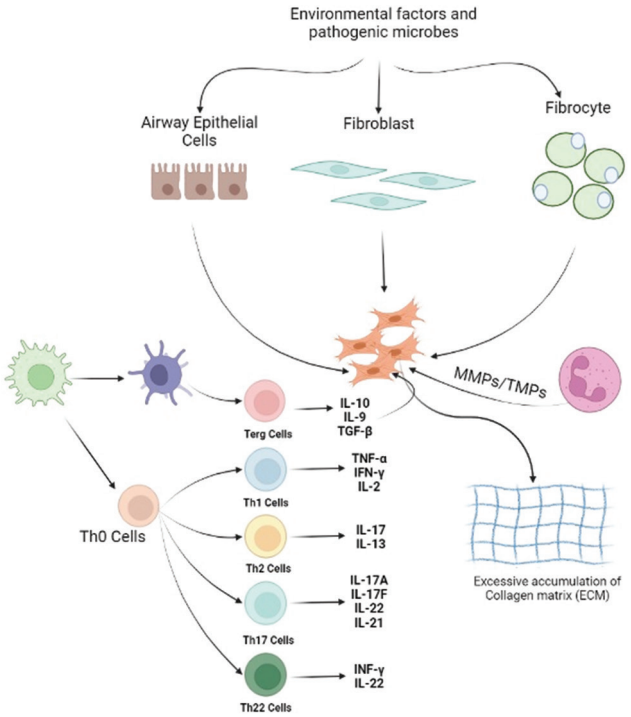

Fig. 3: Immune mechanism in idiopathic pulmonary fibrosis

A new model for the pathogenesis of idiopathic pulmonary fibrosis: Injury by predisposing factor activates multiple inflammatory, cell signaling, and repair pathways. Activation of these cascades causes an imbalance in pro- and anti-fibrotic mediators. In turn, these mediators activate multiple cell types, causing changes in cellular functioning and cell-cell interactions that ultimately result in progressive fibrosis. Th: T-helper cell; CTGF: Connective tissue growth factor; TGF-β: Transforming growth factor-β; PDGF: Platelet-derived growth factor; FXa: Factor Xa; PG: Prostaglandin; IFN-γ: Interferon-γ; and EMT: Epithelial-mesenchymal transition [31].

The growing body of evidence indicates a complex scenario for the development of IPF. The conjunction of distinct genetic architecture, aging-related bio-pathology, and epigenetic reprogramming results in abnormal epithelial cell activation and the initiation/development of IPF[4]. It has been observed that an aberrant recapitulation of developmental pathways induced by tissue-specific stochastic pro-fibrotic age-related epigenetic drifts plays an important role. The epigenome shows a significant drift with age [4].

LONG NONCODING RNA SEQUENCES

Highly transcribed genomes give rise to thousands of long non-coding RNAs (LncRNAs). LncRNAs are highly transcribed RNAs longer than 200 nucleotides that are deficit of translation into proteins. LncRNAs are large and highly heterogeneous collection of transcribed genomes that differs in their biogenesis and genomic origin [33-35].

lncRNA HOXAAS3

lncRNA Hoxaas3 promotes lungs fibroblast activation and fibrosis through miR-450-5p regulating Runx1(36-38). Hoxaas3 being the

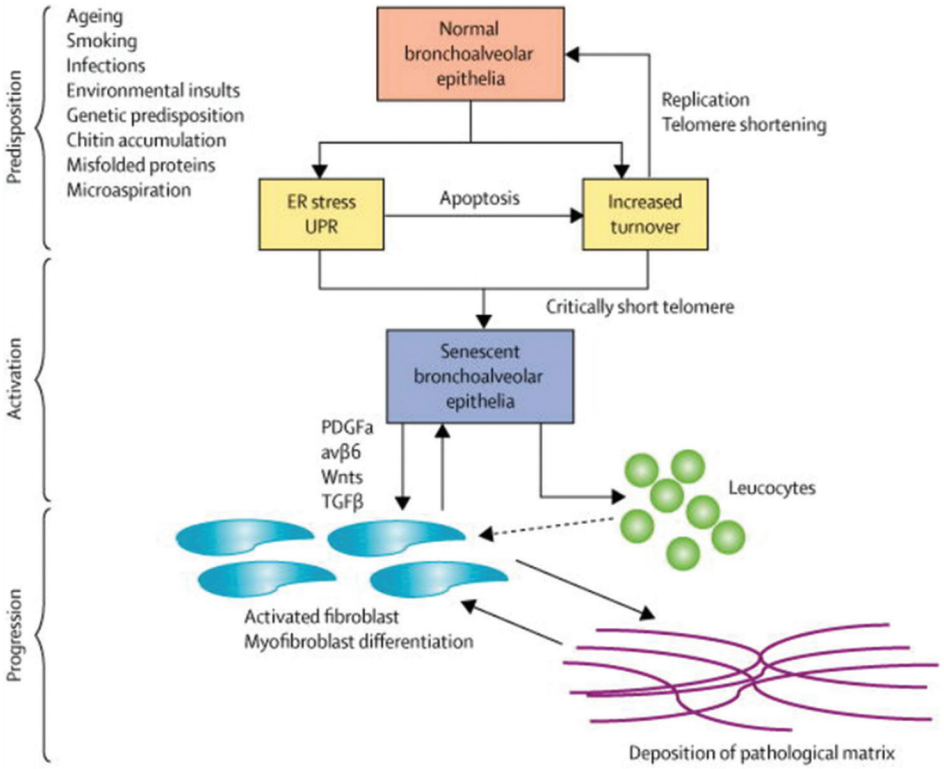

Fig. 4: Three-stage description of the pathogenesis of IPF

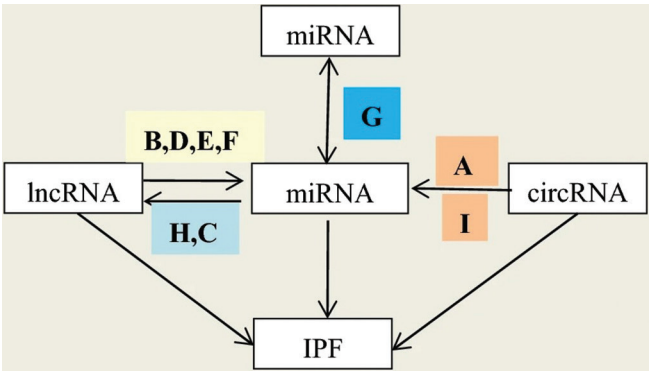

Fig. 5: The role of lncRNA, miRNA, circRNAs, and interplay among ncRNAs in development of IPF.

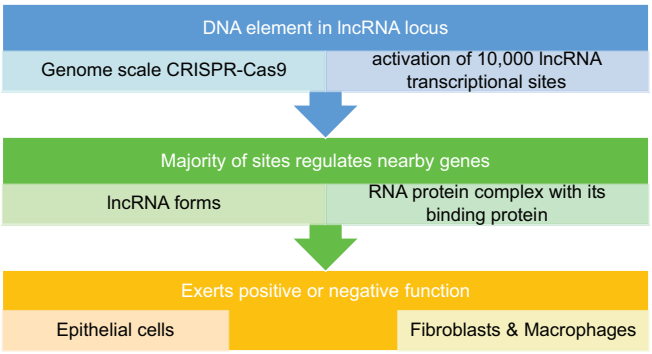

Fig. 6: lncRNA cascades genetically

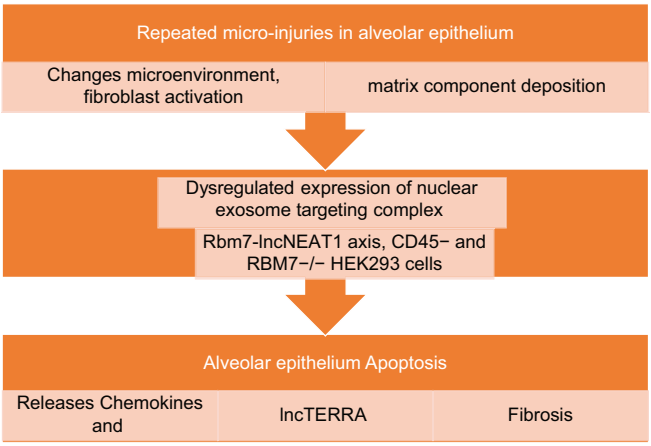

Fig. 7: Epithelial Mechanism of Fibrosis. lncTERRA further accelerates the fibrotic process. It forms a stable complex with the telomere repeat factor TFR2 and telomere DNA and promote fibrogenetic process in lungs

transcriptional target of the TGF-β1/Smad4 pathway, upregulation of Hoxaas3 was recorded in a Bleomycin treated PF model of mice while the knockdown of Hoxaas3 alleviated BLM-induced PF in mice [36-39].

The TGF-β1 family contains of TGF-β isoforms (TGF-β1, β2, and β3, activins and inhibin's, growth differentiation factors (GDFs), bone morphogenetic protein (BMPs), and AMH (anti-Mullerian hormone) ligands specific receptors in tissues forming receptor ligand complexes. This complex formation enables the activation of kinase domains within the receptors which alleviates the phosphorylation cascades of SMAD transcription factors. TGF-β isoforms and activins induce intracellular signaling vial SMAD-2/3 which regulates the expression of several profibrotic genes, plasminogen activator inhibitor-1 (PAI-1), proteoglycans, integrin's, connective tissue growth factor, and MMPs. The release of BMPs through activation of SMAD-1/5/8 enables suppression of TGF-β mediated fibrogenetic gene expression [36,38,40,41] (Fig. 4).

TGF-β enhances fibrosis by differentiation of quiescent fibroblast into matrix secreting myofibroblasts into a protomyofibroblast lineage which under the influence of TGF-β becomes a fully differentiated myofibroblast. TGF-β1 enhances the production of α-smooth muscle (α-SM) actin which provides contractility to myofibroblast. During the increased and upregulated TGF-β1, signals dominate the deposit of myofibroblast excessively in ECM compromising architecture of lungs. TGF-β1 can further exaggerate this action by exhibiting chemoattractant property for some inflammatory immune cells and macrophages [36,38].

The lncRNA Hoxaas3 regulated the fibrogenesis by acting as ceRNA for miR-450b-5p to regulate Runx1 in the lung's fibroblasts being as a transcriptional target of TGF-β1/Smad4 pathway. Further silencing of Hoxaas3 also alleviated IPF *in vitro* as well as *in vivo* proving it as the potential target as well as diagnostic biomarker for IPF [36].

FETAL-LETHAL NONCODING DEVELOPMENTAL REGULATORY RNA (FENDRR)

The initiation and progression of IPF occur due to abnormal activation of lung fibroblasts [42]. The abnormality of the regulation of long LncRNAs in fibrotic lungs was identified by next-generation sequencing analysis. FENDRR expression in ECM of IPF cases and mice with bleomycin-induced pulmonary fibrosis was determined by quantitative real-time PCR and IRP1 (iron-responsive element-binding protein 1). The role of FENDRR in IPF was studied using adenovirus-mediated gene transfer in mice *in vivo*. Downregulation of the expression of FENDRR was observed in fibrotic human and mouse lungs as well as in primary lung fibroblasts isolated from bleomycin-treated mice. TGF-β1 (transforming growth factor-β1)-SMAD3 signaling pathway inhibited FENDRR expression in lung fibroblasts [42-45].

FENDRR is locally found in the cytoplasm of lungs fibroblast in adults, bound with IRP1, suggesting its role in iron metabolism. FENDRR regulates pulmonary fibrosis by the inhibition of fibroblast activation and thus reducing iron concentration and acts as a competitive endogenous RNA of the profibrotic microRNA-214. The BLM-induced lung fibrosis was attenuated by adenovirus-mediated FENDRR gene transfer in the mouse with IPF and improved lung function. The data suggested that FENDRR is an anti-fibrotic long non-coding RNA and a potential therapeutic target for pulmonary fibrosis [46,47].

INHIBITION OF lncRNA PFRL

The lncRNA NONMMUT022554 designated as pulmonary fibrosis-regulatory lncRNA (PFRL) with unknown functions and found that its levels were increased in fibrotic lung tissues of mice and pulmonary fibroblasts exposed to transforming growth factor (TGF)-β1. Furthermore, it was found that enforced expression of PFRL induced fibroblast activation and collagen deposition, which could be mitigated by the overexpression of microRNA (miR)-26a. In some instances, the inhibition of PFRL could significantly escalate the TGF-β1-induced upregulation of fibrotic markers and attenuate fibroblasts growth and differentiation by regulating miR-26a. Meanwhile, the study confirmed that PFRL inhibited the expression and activity of miR-26a, which has been identified as an anti-fibrotic miRNA in our previous study. Interestingly, this molecular study further confirmed that Smad2 transcriptionally inhibits the expression of miR-26a and that the miR-26a/Smad2 feedback loop mediates the profibrotic effects of PFRL in lung fibrosis. Markedly, the knockdown of PFRL ablated bleomycin-induced pulmonary fibrosis *in vivo*. Taken together, the findings indicated that lncRNA PFRL contributes to the progression of lung fibrosis by modulating the reciprocal repression between miR-26a and Smad2 and that this lncRNA may be a therapeutic target for IPF [15,48,49].

lncRNA PFAR AS A NEW PRO-FIBROTIC TARGET

The lncRNA NONMMUT065582, designated pulmonary fibrosis-associated RNA (PFAR), is found to be upregulated in the lungs of mice's with pulmonary fibrosis as well as in fibrotic lung fibroblasts areas. Hyper-expression of PFAR alleviated fibrogenesis through regulation of miR-138 and knockdown of PFAR resulted TGF-β1-induced fibrogenesis in lung fibroblasts. Besides, knockdown of miR-138 promoted fibrogenesis by targeting regulation of yes-associated protein 1 (YAP1), whereas enhanced expression of miR-138 attenuated fibrogenesis in lung fibroblasts. Normally, PFAR being a competitive endogenous RNA (ceRNA) of miR-138, the forceful expression of PFAR reduced the expression, function, and activity of miR-138 to activate YAP1 and thus ablated fibrogenesis in lung fibroblasts, whereas loss of YAP1 escalated the reduction of pro-fibrotic effect of PFAR. Prominently, PFAR silencing alleviated BLM-induced lung fibrosis in mice. Together, outcomes evidence lncRNA PFAR as a new pro-fibrotic target that acts as a ceRNA of miR-138 during lung fibrosis and demonstrated PFAR as a novel therapeutic target for the prevention and treatment of lung fibrosis [16].

KNOCKDOWN OF lncRNA DLEU2

The lncRNA DLEU2 increased expression was found in the fibroblasts tissues of BLM-induced fibrosis in mice. The level of expression of DLEU2 and TRIM2 was increased along decrease in expression of miR-369-3p in TGF-β1-stimulated A549 cells and fibrotic tissues of BLM-induced fibrosis ice. The knockdown of DLEU2 was found to suppress IPF by increasing the level of miR-369-3p and TRIM2. The results suggested that the negative modulation of DLEU2 can be a novel therapeutic target for IPF in the future [50].

The previous study was done by Yi *et al.,* 2021 reported that the DLEU2 inhibits the migration and proliferation of epithelial mesenchymal transition (EMT) in A549 cells of bleomycin-induced fibrosis. The expression of miR-369-3p was decreased in mice lung tissue while increasing the expression of TIRM2. The bleomycin-induced lung fibrosis was stimulated TGF-β1 in A549 cells. The study stated that DLEU2 inhibits the IPF through upregulating of miR-369-3p expression results to suppress the TRIM2 [51].

TERRA EXPRESSION IN IPF

The lncRNA Telomeric repeat containing RNA (TERRA) can partially explain the cause of IPF. TERRA offers the regulatory mechanism in pathogenesis of IPF [52]. The dysregulation of expression of TERRA in IPF cases can be sensitive to oxidative stress or apoptosis in AEC Type 2 cells by causing the mutation of TERRA at the promoter CCAAT-box (GCAAT) *in vitro*. The disruption leads to reduced TERC levels, lower telomerase activity, and short telomeres that can induce IPF [53-55].

MOLECULAR MECHANISM OF LncRNAs IN IPF

The circRNAs produces miRNA sponges to repress targeted genes while LncRNAs generates miRNA sponges to regulate the gene expression cascade for causing IPF. The miRNAs influence the expression on LncRNAs by regulating methylation of LncRNAs promoter as well as regulates expression of miRNAs through various proteins. The LncRNAs act as miRNA precursor and offer competitive binding for target genes by LncRNAs as well as miRNAs. The regulation of miRNAs occurs through complementary binding process in the target gene where miRNAs increase the degradation of LncRNAs and revealing the function of miRNAs transporters by circRNAs [56-58] (Fig. 5) .

lncRNAs can interact with miRNA. lncRNA consists of DNA element that is more prominent source for regulation than the whole lncRNA itself. In IPF, lncRNAs are involved in the pathogenic development of fibrosis by specific mechanisms in various cells like epithelial cells, fibroblasts, and macrophages [14,58,59] (Figs. 6 and 7).

lncRNA MEDIATING IPF THROUGH EPITHELIAL CELLS

Suppressing proliferation and migration of lung fibroblast cells

lncRNA lacks the ability of coding protein and seems to lack bio-function but plays a critical role in regulating gene expression through variety of mechanism. It has been observed high expression of lncRNA SNHG16 in BLM-induced IPF where SNHG16 directly targeted miR-453-3p in turn decreasing the level of Notch2. lncRNA SNHG16 aids IPF by directly acting in miR-455-3p regulating Notch2 pathway. Knockdown of SNHG16 attenuated BLM-induced IPF while lungs fibroblasts treated with TGF-β1 when transfected with sh-SNHG16 showed dramatic increase in proliferation [34,60]. Knockdown of SNHG16 studied by wound healing assay and TGF- β1 showed decrease in proliferation and migration of lung fibroblast cells by regulating the expression of Notch2 as well as α-ASM, E-cadherin, Collagen 1, and Fibronectin 1 [34,61].

lncRNA has matured as critical factors for regulation of many homeostatic processes during organ fibrosis. The key lncRNA CTD-2528l19.6 had higher expression in early stage IPF and reduced expression in advanced stage IPF compared to normal tissue. lncRNA CTD-2528l19.6 has been responsible for control of fibroblast activation in progression and proliferation of IPF by mediating the expression fibrosis-related genes LRRC8C, DDIT4, THBS1, S100A, and TLR7. In a study, lncRNA CTD-2528l19.6 was silenced reveled the increased expression of Fn1 and Collagen I at mRNA and protein levels thus enhancing the transition of fibroblast into myofibroblast as well as accelerated the progression, proliferation, and metastasis of MRC-5 cells [62-64].

Higher expression of lncRNA CTD-2528l19.6 alleviated fibroblast activation at MRC-5 cells of IPF induced by TGF-β1. lncRNA CTD-2528l19.6 prevents the progression of IPF from early stage and inhibits the activation of fibroblast in advanced stage by regulating the expression of LRRC8C genes [62].

The lncRNA ZEB1 is a key positive regulatory factor in EMT as a direct exogenous target of miR-141-3p which can be suppressed by TGF-β1 and the up regulatory effect of miR-141-3p inhibited EMT by acting on ZEB1. The silencing process of lncRNA ZEB1-AS1 inhibited BLM-induced pulmonary fibrosis by the suppression of EMT progression [65,66]. Mechanistically, ZEB1-AS1 influences IPF by regulating the expression and function of ZEB1 and instigating EMT of alveolar Type II epithelial cells by competitively binding miR-141-3p [56]. The positive regulatory effect as well as inhibition of BLM-induced fibrosis by silencing of

Table 1: Summary of lncRNA involved in disease condition of Lungs (14)

Lung disease	lncRNA	Mechanism of Action
Ali	FOXD3-AS1	FOXD3-AS1 serves as sponge for miR-150, inhibiting lung epithelial cell growth
	CASC2	Serves as miR-144-3p decoy and plays a role in LPS induced lung epithelial cell apoptosis
	NANCI	Involved in the development of hypoxia induced lung injury
IPF	H19	Upregulated in fibroblasts, promoting proliferation and collagen deposition
COPD	SCAL1	Upregulated in response to cigarette smoke to serve as protective mechanism
Lung Cancer	MALAT1	Upregulated in NSCLC and predictor of prognosis
	UCA1	Upregulated in NSCLC and predictor of prognosis
	HOTAIR	Upregulated in NSCLC and promotes metastatic breast cancer progression
PAH	TCONS_0034812	Downregulated in PAH patients, promoting proliferation of PASMCs and pulmonary artery thickening

lncRNA ZEB1-AS1 makes it a novel therapeutic target for the prevention and treatment of IPF [66,67].

The implication of lncRNA in IPF (Table 1)

The majority of human genome is pre-occupied by variety of non-coding genes and has recently garnered increased attention for their implications in a various disease condition. This review tries to emphasize and bring forward the current scientific society and growing number of evidence concerning long non-coding RNA regulation and their functional roles in pathogenesis and treatment of IPF. These lncRNA and mRNA have similar fashioned process of biogenesis and regulatory processes such as capping, polyadenylation, post-transcriptional modifications, and exonuclease degradation [68,69]. Uncontrolled release oflncRNAs occur in lung diseases such as acute epithelial lung injury, IPF, COPD, lung cancer, and pulmonary arterial hypertension. Some of the lncRNAs have well known functions while the overwhelming majority of this group requires further research to completely understand [70].

Acute epithelial lung injury and acute respiratory distress syndrome (ARDS) have higher rate of mortality and morbidity [71,72]. With advancing number of evidence, it is seen that FOXD3-AS1 promoted oxidative stress-induced lung epithelial necrosis during hyperoxia-induced acute lung injury where FOXD3-AS1 mediates as a competing endogenous non-coding RNA for miR-150, leading to inhibition of growth and differentiation as well as alveolar epithelial cell death [73]. Similarly, a study using lipopolysaccharide (LPS)-induced ALI murine model had shown lncRNA CASC2 functions as a miR-144–3p decoy and plays a critical role in LPS-induced lung epithelial cell apoptosis [74]. Long non-coding RNA NANCI has been reported to be involved in the development of hyperoxia-induced lung injury in neonatal mice [75]. These findings indicated the dysregulation of lncRNAs in the pathogenesis of ALI/ARDS and potentially would help to identify novel mechanisms and/or therapeutic strategies in the future [76,77].

Interferon-γ (INF γ) [78], Etanercept [79], Bosentan [80], Macitentan [81], Sildenafil [82], and Imatinib [83] had produced the negative. The triple therapy with drugs prednisolone, azathioprine, and NAC produced potentially harmful effects, and drugs such as ambrisentan [84], everolimus [85], and warfarin [86] resulted in rapid progression of the disease or increased risk of mortality.

Two of the drugs Pirfenidone (with non-well-established mechanism) and Ninetadanib (an intracellular inhibitor that targets multiple tyrosine kinases including VEGF and FGF as well as PDGF are approved for the treatment of IPF as disease modifying therapy in the United States [87].

The newer therapy for age-related cases of IPF localizes key cellular mechanisms in aging cells. Dasatinib, quercetin, and navitoclax are senolytic drugs. Dasatinib and quercetin exhibit senolytic activity by the inhibition of tyrosine kinases whereas navitoclax blocks the anti-apoptotic protein family members of the B-cell lymphoma 2 (BCL-2) [87,88]. The secretory associated senescence phenotype (SASP) which is regulated by the competitive targeting of rapamycin mTOR inhibitor. It can decrease the level of SASP factors in senescent fibroblasts. mTOR inhibitors such as rapamycin also promotes the process of autophagy and the apoptosis of fibroblasts in lungs with IPF. Rupatadine is also responsible for regulation of cellular senescence and exaggerates SASP by preventing the activation of p53–p21 pathway by the regulation of expression of CCAAT/enhancer-binding protein-β (C/EBPβ), a positive modulator of SASP [87]. SASP can also be downregulated by the inhibitors of the nuclear factor (NF)-κB signaling pathway. The certain changes found in the AEC suggest that activator of sirtuin 3 (SIRT3) and mitophagy inducers along with process to increase levels of mitochondrial DNA (mtDNA) repair enzymes might be advantageous in due treatment process of IPF. The drugs such as raloxifene and some androgens with estrogen receptor modulation activity can be applied to elongate the length and for inducing telomerase activity [89].

CONCLUSION

IPF is a rare, nexus, age-related, and epithelial-driven fibrotic condition of lungs. The disease is progressive and lethal, usually within few years of diagnosis with limited therapeutic options with the two approved drugs that also reduce the pace of development of the disease. From the aggregated scientific evidences from the past two decades, several meaningful pathogenic pathways have been recognized that have the potential to become the novel target for therapy. The identification of involvement of alveolar epithelial cells and their part in the pathogenesis of IPF, their effects on fibroblasts, and extracellular matrix comes under the radar of therapeutic approaches.

Apart from the understandings and interpretations of pulmonary tissue regeneration and remodeling of IPF tissues, some positive outcomes can be seen in the studies intervening lncRNAs role in IPF in preclinical animal models which have led to substantial advances in inpatient therapy. However, most research is concentrated into putative therapies for IPF and prominently focused on drugs that inhibits immune molecules and mediators affecting proliferation, migration, and differentiation of fibroblasts into activated myofibroblast.

Normally, there are stronger evidences that support the involvement of aging as a prominent risk factor for IPF but still there are some questions that need to be answered like the mechanisms that lead to SASP and senescence of epithelial cells and fibroblasts which are still undefined. The growing recognition and understanding of commonly occurring gene variants and rare gene variants associated with IPF, epigenetic reprogramming and age-related molecular changes, have given novel therapeutic approaches for the management of IPF, including eliminating senescent cells, attenuating SASP, regulating miRNAs, improving mitochondrial function and proteostasis, and changing the patterns of DNA methylation and histone de-acetylation with the help of lncRNAs.

With recent advances in study related to epigenetic and RNA sequencing, the diverse cellular processes implicated in aging biology, including cellular senescence with lncRNAs contributed to the pathogenesis of IPF and COPD. The enhanced level of expression of lncRNAs was found in several studies in patients with IPF. In addition, increased expression of the lncRNAs and miRNAs in the lungs of IPF is landmarks and applied as a biomarker for the diagnosis of IPF and COPD. The studies also revealed the adenovirus-mediated FENDRR gene transfer, adenovirus-mediated miR-101 gene transfer, lncRNA PFAR, and lncRNA (PFAL) expression reduced the progression of IPF, as well as improved lungs, function in an animal model of IPF induced by bleomycin in Mice. The understanding of the pathogenesis of IPF has advanced substantially and targeting the lncRNAs dysregulation can be a potential target for the treatment of IPF.

AUTHOR CONTRIBUTION

All authors have equal contribution in this manuscript.

CONFLICT OF INTEREST

There is no any conflict of interest.

AUTHORS FUNDING

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