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Role of Epigenetic Mechanisms in Lung Fibrosis: Therapeutic Opportunities and Challenges

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Abstract

Lung fibrosis poses a serious risk to one's health since it might result in respiratory failure due to an abnormal accumulation of fibrotic tissue in the lungs. Epigenetic mechanisms, such as histone changes, DNA methylation, and non-coding RNAs, closely control gene expression patterns and cellular processes associated with lung fibrosis. Anomalies in DNA methylation patterns connected to changes in gene expression profiles and disturbances in fibrotic signaling pathways are potential targets for diagnosis and treatment in fibrotic lungs. A portion of the abnormal gene expression patterns and decreased cellular activity observed in fibrotic lungs can be explained by hepatocellular dysregulation. Non-coding RNAs have an impact on crucial signaling pathways that cause lung fibrosis to develop. MicroRNAs (miRNAs) and long non-coding RNAs (lncRNAs) are two examples of these routes. Collaboration between medical professionals, researchers, regulators, and the advancement of pulmonary fibrosis precision medicine therapies depends on industry actors. Recent developments in the CRISPR-Cas9 system have enabled epigenetic editing. This study examines the benefits and drawbacks of using these modifications for medical treatment. A few concerns need to be fixed before epigenetic therapies may be used effectively in clinical settings. Delivery, specificity, off-target repercussions and morality are some of these challenges. The goal of this review is to enhance patient outcomes and quality of life by investigating the intricate relationship between epigenetic modifications and the biology of lung fibrosis.

Keywords: Lung fibrosis, epigenetics, DNA methylation, histone modifications, non-coding RNAs, therapeutic intervention

INTRODUCTION

Lung fibrosis is a progressive and often fatal condition that encompasses a group of interstitial lung diseases characterized by the abnormal accumulation of fibrotic tissue in the lungs. This fibrotic tissue formation disrupts the normal architecture of the lungs, impairs gas exchange, and ultimately leads to respiratory failure [1]. Idiopathic pulmonary fibrosis (IPF) is one of the most well-known and severe forms of lung fibrosis, with a median survival time of only 2–3 years post-diagnosis [2]. Lung fibrosis comprises a complex interplay of several cellular and molecular pathways that develop and progress. Repeated lung tissue injuries that result in dysregulated healing processes and excessive fibrotic remodeling are hypothesized to be the etiology of lung fibrosis [3] Lung fibrosis can arise due to various causes such as autoimmune diseases, infections, genetic predisposition, and environmental variables that include exposure to chemicals, pollutants, infections, and drug reactions [4–6]. Other genetic factors highly influence the pathogenesis of lung fibrosis, like DNA methylation, histone modification, and upregulation and downregulation of genes involved in fibrosis pathways and fibrotic tissue remodeling [7–9]. In addition to genetic and epigenetic factors, some other non-genetic factors are also responsible for

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disease development and progression, for example, gastroesophageal reflux disease (GERD). GERD is characterized by the reflux of stomach acid into the esophagus and has been identified as a potential risk factor for lung fibrosis [10]. Along with these, exposure to industrial chemicals, environmental pollutants, and cigarette smoke can induce lung fibrosis by triggering inflammation and oxidative stress [11–12] (Figure 1).

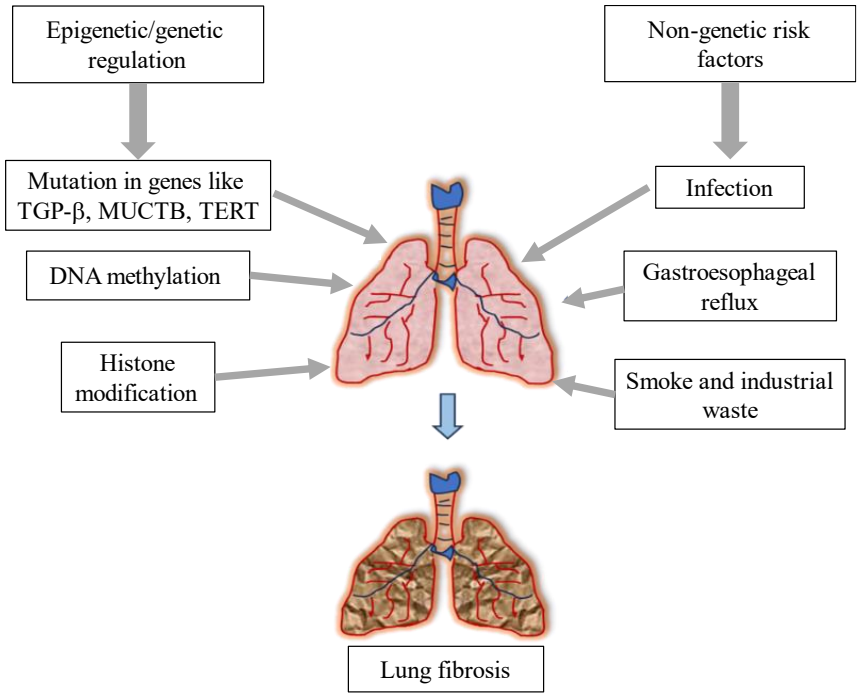

Figure 1. The image shows the various factors that affect the lungs and lead to the development of fibrosis.

Lung fibrosis poses a significant burden on both patients and healthcare systems worldwide. The disease not only reduces patients' quality of life due to progressive dyspnea and exercise intolerance but also imposes substantial economic costs related to hospitalizations, medical interventions, and lost productivity. Moreover, the prognosis of patients with lung fibrosis is very poor and limited treatment options are available to slow the disease progression. Consequently, there is an urgent need to understand better the underlying mechanisms driving lung fibrosis and to develop more effective therapeutic strategies.

EPIGENETICS AS A REGULATORY MECHANISM

Epigenetics is defined as heritable modifications in gene expression that take place without changes to the underlying DNA sequence. DNA methylation, histone modifications, and non-coding RNAs are examples of epigenetic alterations that are essential for controlling cellular processes and gene expression patterns. There has been growing evidence that suggests that disruption of epigenetic pathways has a role in the pathophysiology of several diseases, such as lung ailments, cardiovascular diseases, and cancer [13–15]. A study reported that these alterations are essential for regulating chromatin structure and gene accessibility, which regulates gene expression patterns and cellular phenotypes [16]. Recently, the focus on understanding the function of epigenetics in pulmonary fibrosis has been spiked. Epigenetic modifications, specifically DNA methylation and histone modifications, have been related to the regulation of the significant fibrotic signaling pathways along with the expression of genes involved in extracellular matrix formation, immunological response, and tissue repair [9, 17]. The presence of altered DNA methylation patterns in fibrotic lungs raises the possibility that these changes play a role in disease pathogenesis [18]. Similar to this, abnormal gene expression profiles seen in lung fibrosis have been linked to dysregulated histone modifications [19]. In lung

fibrosis, emerging research has highlighted the importance of epigenetic modifications in driving fibroblast activation, ECM remodeling, inflammation, and aberrant signaling pathways implicated in disease progression. An understanding of the function of epigenetic pathways in pulmonary fibrosis may offer important insights into the disease's pathophysiology, possible diagnostic indicators, and novel treatment options [20]. Epigenetic changes can be reversed, allowing for targeted therapy aimed at enhancing fibrotic processes and reinstating typical gene expression patterns. The complex connection and crosstalk between epigenetic alterations and lung fibrosis can help researchers discover novel molecular targets and advanced tools for diagnosing, predicting, and treating the condition. The interaction between DNA methylation and histone modifications has revealed the complex relationship between these epigenetic mechanisms in lung fibrosis [21]. Some recent studies suggested that the crosstalk between DNA methylation and histone modifications is essential for the regulation of gene expression and cellular functions in lung fibrosis [22]. Recruiting histone-modifying enzymes or proteins that detect methylated DNA can directly affect histone modifications. Vice versa, changes in histone levels can influence DNA methylation patterns by influencing the way that DNA methyltransferases or demethylases bind to particular genomic locations [23].

However, research has also suggested that non-coding RNAs such as microRNAs and long non-coding RNAs are essential for regulating the interplay between histone modifications and DNA methylation [24, 25]. These non-coding RNAs can interact with histone-modifying enzymes and DNA methylation mechanisms, influencing chromatin structure and gene expression profiles in lung fibrosis. It is reported that long non-coding RNAs (lncRNAs) can modify gene expression at the transcriptional level by interacting with chromatin-modifying complexes [25]. They can act as scaffolds to recruit histone methyltransferases or histone deacetylases, histone-modifying enzymes, to specific genomic loci, altering the chromatin structure and gene expression. Dysregulated expression of certain long non-coding RNAs can promote the activation of fibroblasts and the deposition of extracellular matrix proteins, contributing to fibrotic tissue remodeling and leading to lung fibrosis. This study covers the current level of our understanding of the role of epigenetics in lung fibrosis and focuses on various aspects, such as the interactions between significant fibrotic signaling networks, dysregulated cellular activities, identification of possible therapeutic targets, prognostic markers and diagnostic markers in lung fibrosis, and the impact of histone modifications and DNA methylation on gene expression and cellular phenotypes linked to lung fibrosis [26–34].

Epigenetic Regulation of Fibrotic Genes and Pathway

It has been discovered that lung fibrosis causes DNA methylation alterations in several fibrosis-related genes and signaling pathways. For instance, DNA methylation controls the major profibrotic cytokine TGF-1 (Transforming Growth Factor-beta 1) in lung fibrosis [35]. According to research decreased gene expression brought on by hypermethylation of the TGF-1 promoter region can affect the control of fibrotic processes. Similar to this, it has been discovered that lung fibrosis causes DNA methylation alterations in several fibrosis-associated genes, including connective tissue growth factor (CTGF), matrix metalloproteinases (MMPs), and tissue inhibitors of metalloproteinases (TIMPs) [36]. Global changes in DNA methylation patterns can have significant implications on cellular functions and signaling networks linked to lung fibrosis, in addition to gene-specific DNA methylation modifications. Numerous differentially methylated regions (DMRs) in fibrotic lungs as compared to healthy lungs have been identified by epigenome-wide DNA methylation profiling studies [37]. These DMRs frequently reside in the regulatory regions of genes involved in immunological response, extracellular matrix formation, fibroblast activation, and inflammation, demonstrating the extensive influence of DNA methylation on the pathophysiology of lung fibrosis. The imbalance between DNMTs and DNA demethylases, the enzymes responsible for removing methyl groups from DNA, is thought to be the cause of the dysregulation of DNA methylation in lung fibrosis. As reported in fibrotic lungs, the expression of DNMT and DNA demethylase becomes altered, which tells us their role in unusual DNA methylation patterns. There are other factors like smoke and air pollutants that come under as environmental factors and may induce lung fibrosis.

DNA METHYLATION IN LUNG FIBROSIS

DNA methylation is one of the most important ones of epigenetic modification areas and is supposed to play a key role in the regulation and deregulation of candidate gene expression in many diseases, including lung fibrosis. As stated above, in the lungs, there are so many factors for the induction of scar accumulation. These factors could be genetic or environmental, which disrupt lung tissue architecture, thereby leading the lung to perform abnormal functions [26, 27].

In DNA methylation, methyl group would be added to DNA; due to this, candidate gene expression for lung fibrosis can be regulated [26–28]. Furthermore, candidate genes of inflammation, fibroblast activation, and tissue remodeling associated with lung fibrosis can be controlled with DNA methylation modifications [29]. Knowing the involvement of candidate genes by DNA methylation in the induction of lung fibrosis may provide valuable scope to the scientist's insight into its therapeutic purposes. However, for the diagnosis of lung fibrosis, again understanding the role of DNA methylation in lung fibrosis is vital to identifying the potential biomarkers [30]. Therefore, identifying and pointing to an abnormality in DNA methylation patterns may be future for the patient's treatment.

Alterations in DNA methylation may affect the activation and cytokine production of immune cells, such as macrophages and T cells, to regulate fibroblast activation and extracellular matrix remodeling processes [31]. The addition of a methyl group to the cytosine residues in the CpG dinucleotides (CpG island) of DNA is known as DNA methylation. DNA methyltransferase enzymes (DNMTs) catalyze this modification, suppressing the expression of genes by inhibiting the binding of transcription factors and other regulatory proteins to DNA [31, 32]. Studies have also reported that people with fibrotic lung diseases have dynamically changing DNA methylation patterns in their lungs. In fibrotic lung tissue, global DNA hypomethylation, or a decline in overall DNA methylation levels, has been noted. On the other hand, reports have also been made of site-specific DNA hypermethylation, which involves enhanced methylation of particular genes or regulatory areas. Lung fibrosis is thought to be caused by dysregulated gene expression and altered cellular processes, both of which are related to these alterations in DNA methylation patterns [29, 34].

Additionally, recent studies have suggested that other epigenetic modifications, such as histone modifications and non-coding RNAs, may affect lung fibrosis-related DNA methylation modification. These epigenetic codes, the crosstalk between DNA methylation and histone modifications is one of the crucial players in regulating gene expression. The alterations of DNA methylation and dysregulation of gene expression patterns in lung fibrosis can be associated with histone modifications, including acetylation and methylation.

DNA Methylation: Diagnostic and Therapeutic Implications

Changes in DNA methylation patterns in lung fibrosis offer potential as diagnostic and prognostic markers, aiding in early detection and personalized treatment strategies. Unique methylation signatures associated with fibrotic lung diseases may facilitate precise diagnosis and shed light on disease heterogeneity. As it is discussed earlier and shown in Figure 2, the process of DNA methylation takes place using of DNA methyltransferase (DNMT). DNA methyltransferase catalyzes the addition of methyl groups to cytosine residues within DNA molecules leading to the transformation of cytosine into 5'-methyl-cytosine on GC-rich CpG motifs [38]. Research suggests DNA methylation as a therapeutic target in lung fibrosis [26]. Preclinical studies using DNMT inhibitors show promise in reversing fibrotic markers and improving lung function [39, 40]. However, challenges regarding specificity, efficacy, and safety need addressing. Epigenetic changes in various lung cell types, including fibroblasts, epithelial cells, and immune cells, contribute to fibrogenesis. Targeting DNA methylation alterations in these cells holds therapeutic potential, as evidenced by animal models using DNMT inhibitors. Careful consideration of off-target effects and long-term consequences is vital for the development of safe and effective epigenetic-based therapeutics in lung fibrosis.

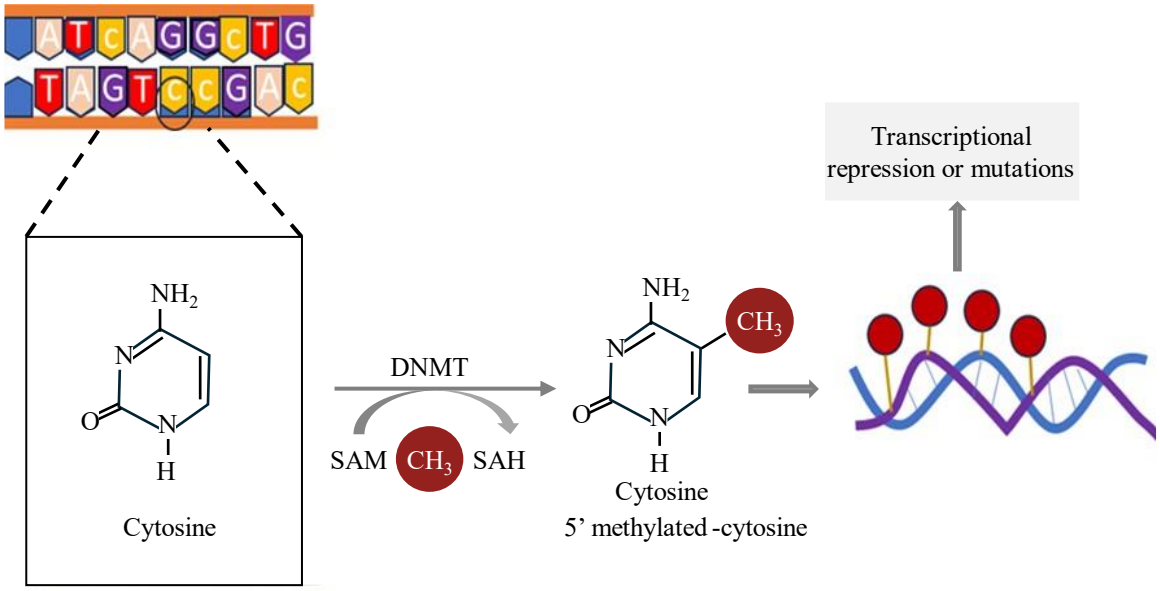

Figure 2. The diagram illustrates the process of DNA methylation, wherein cytosine is transformed into 5'-methyl-cytosine through the enzymatic activity of DNA methyltransferase (DNMT). DNA methylation predominantly takes place at cytosines adjacent to guanine residues, known as CpG motifs. Here, SAM= S-adenosylmethionine; SAH= S-adenosylhomocysteine. Figure Created with BioRender.com

To sum up, DNA methylation plays a crucial role in regulating gene expression and physiological processes in lung fibrosis. Understanding its dynamic changes offers insights into disease pathophysiology, diagnostic markers, and therapeutic targets, paving the way for novel treatment approaches. Further investigation into specific genes and regulatory regions affected by DNA methylation changes is warranted to advance our understanding of lung fibrosis epigenetics.

HISTONE MODIFICATIONS IN LUNG FIBROSIS

Histone modifications play a pivotal role in regulating gene expression and cellular functions implicated in lung fibrosis progression. Dysregulated histone changes contribute to abnormal gene expression profiles and impaired cellular functions observed in fibrotic lungs [9]. Histones, crucial for DNA organization, undergo post-translational modifications such as acetylation, methylation, phosphorylation, and ubiquitination, which dynamically modulate chromatin structure and gene accessibility [41]. Dysregulation of histone-modifying enzymes, including histone acetyltransferases (HATs), histone deacetylases (HDACs), histone methyltransferases (HMTs), and histone demethylases (HDMs), disrupts these alterations. In lung fibrosis, histone modifications are associated with fibroblast activation, excessive extracellular matrix formation, and dysregulated immunological responses [22, 42]. As illustrated in Figure 3, the histone modification takes place by recruiting Histone Acetyl Transferases (HATs), which results in the transfer of acetyl groups from acetyl-CoA to specific lysine residues on histone proteins. This process results in the relaxation of chromatin and is available to bind with transcription factors and RNA polymerase II (RNAPII) [43]. The methylation and acetylation depend on the open or condensed chromatin. In the case of chromatin opening, it facilitates the activation of transcription while condensed chromatin using histone methylation, catalyzed by Polycomb Repressive Complex 2 (PRC2) using S-adenosylmethionine (SAM) as the methyl group donor, leads to chromatin condensation and repress the gene transcription [43]. Histone methylation may contribute to reducing the expression of genes associated with anti-fibrotic pathways or the increasing of pro-fibrotic gene expression patterns, in lung fibrosis.

Histone acetylation, primarily controlled by HATs and HDACs, influences chromatin accessibility, impacting gene activation and repression [22]. HDAC inhibitors show promise in preclinical models by

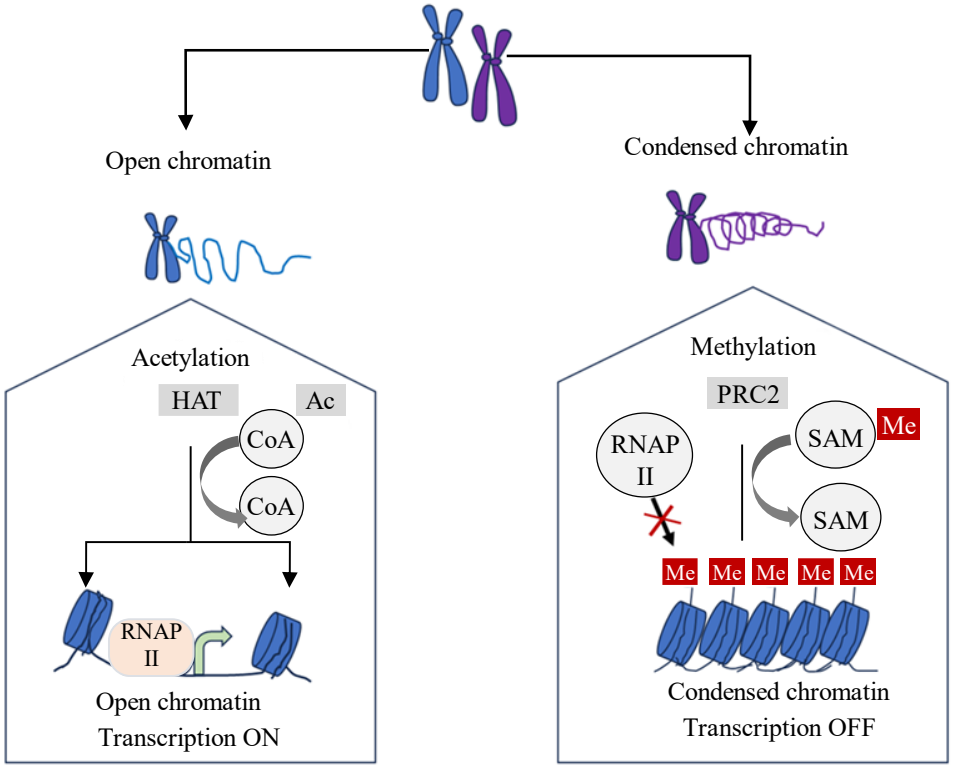

Figure 3. The image shows Histone acetylation, performed by Histone Acetyl Transferases (HATs) by using acetyl-CoA as a donor, leading to chromatin opening that allows RNAPII to bind to a promoter to induce target gene expression. Conversely, histone methylation, performed by Polycomb Repressive Complex 2 (PRC2) by using SAM as the donor, leads to chromatin closing and represses transcription by preventing RNAPII binding.

restoring histone acetylation patterns and attenuating fibrotic characteristics. Histone methylation patterns also play a crucial role. Elevated levels of H3K9 and H3K27 methylation, coupled with reduced H3K4 and H3K36 methylation, are associated with gene repression and aberrant repair mechanisms in fibrotic lungs [44]. The balance between histone methyltransferases and demethylases regulates these patterns. Other modifications, like phosphorylation and ubiquitination, are linked to pro-fibrotic gene activation and chromatin remodeling in lung fibrosis [22]. The interplay and crosstalk between histone modifications, regulated by various histone-modifying enzymes and non-coding RNAs, may influence gene expression dynamics of various pathways and diseases, suggesting that targeting histone-modifying enzymes holds therapeutic potential [39, 45]. It has already been reported that HDAC inhibitors can improve lung function by restoring histone acetylation patterns, while histone methyltransferases or demethylases require further investigation for therapeutic efficacy [45]. Histone modifications provide an understanding of lung fibrosis pathophysiology and offer possible therapeutic targets. More research and understanding are required to fully expose the complex epigenetic processes driving histone modifications, safety evaluation and efficacy of targeting histone-modifying enzymes in lung fibrosis treatment.

NON-CODING RNAs

Non-coding RNAs (ncRNAs) are a diverse class of RNA molecules that play a role in regulating gene expression and cellular processes but do not encode [15]. Recent research has highlighted the involvement of non-coding RNAs, including long non-coding (lncRNAs) RNA and microRNA (miRNAs), in the pathogenesis of pulmonary fibrosis and disease prognosis. Long non-coding RNAs (lncRNAs) are 200 nucleotides or longer RNA transcripts that regulate gene expression through various mechanisms such as chromatin remodeling, transcriptional regulation, and post-transcriptional processing.

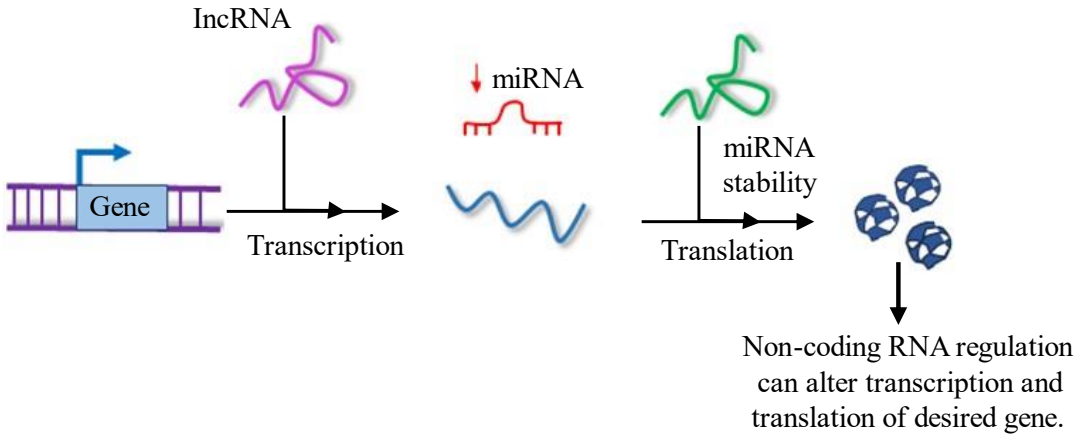

Figure 4. The picture illustrates how microRNAs (miRNAs) and long non-coding RNAs (lncRNAs) work together to inhibit the transcription of a target gene.

Dysregulation of lncRNAs has been involved in the development and progression of lung fibrosis [46, 47]. For example, some lncRNAs have shown a contribution to fibrotic tissue remodeling and lung dysfunction by regulating the expression of genes involved in fibroblast activation, extracellular matrix deposition, and inflammation. Long non-coding RNAs (lncRNAs) may regulate gene expression through acting as molecular decoys, scaffolds, or guides for chromatin-modifying complexes [48]. As shown in Figure 4, these lncRNAs and miRNAs can interact with chromatin-modifying complexes, such as histone methyltransferase or histone deacetylase and induce repressive chromatin modifications at the promoter region of the target gene, leading to chromatin condensation and transcriptional repression [48].

MicroRNAs (miRNAs) are small, single-stranded RNA molecules approximately 22 nucleotides in length that post-transcriptionally regulate gene expression by binding to the 3' untranslated region (UTR) of target mRNAs, leading to mRNA degradation or translational repression. Aberrant expression of miRNAs has been observed in pulmonary fibrosis and has been associated with various aspects of the disease, including fibroblast proliferation, epithelial-mesenchymal transition (EMT), and immune dysregulation and targeting it can be a potential therapeutic option [49, 50]. Certain miRNAs have been identified as potential biomarkers for pulmonary fibrosis diagnosis and prognosis, while others represent therapeutic targets for intervention. microRNAs (miRNAs) primarily function post-transcriptionally by binding to the 3' untranslated region (UTR) of target mRNAs, leading to mRNA degradation or translational repression. Certain miRNAs may target transcripts encoding proteins critical for fibrotic processes, such as transforming growth factor-beta (TGF-β) signaling components or extracellular matrix proteins [51, 52].

Non-coding RNAs can modulate various signaling pathways implicated in lung fibrosis pathogenesis. For example, certain lncRNAs or miRNAs may regulate the activity of key signaling pathways, such as TGF-β signaling, which plays a central role in fibroblast activation and extracellular matrix deposition. In general, the impact of non-coding RNAs on lung fibrosis is developed by studying various processes including transcriptional and post-transcriptional mechanisms, DNA modifications, and molecular signaling pathway modulation. It is also to be noted that by understanding the role of ncRNA on lung fibrosis may provide some help towards its therapeutic intervention and insights into the molecular processes of the disease [50–52].

EPIGENETIC THERAPIES FOR LUNG FIBROSIS

There are limited options available for the treatment of lung fibrosis. There is only one medicine whose role is helpful in the treatment of pulmonary fibrosis, and that is Pirfenidone. This drug is used for the treatment of idiopathic pulmonary fibrosis. However, its long-term effects on the patient are now

well known. Therefore, there is an urgent need for an alternative option for the treatment of lung fibrosis. Recently only, the role of epigenetics and its modifications (DNA methylation, non-coding RNA, etc.) has provided some hope in addressing the complex pathogenesis of the lung.

Targeting DNA Methylation for Therapeutic Purposes

So, it is now known that abnormal DNA methylation may be one of the causes of lung fibrosis, with generating deregulating genes involved in fibrotic processes and targeting DNA methylation may further help in reversing the same. It is further to be noted that DNA methyltransferase inhibitors (DNMTis), which could be a 5-azacytidine and decitabine have the potential to reverse the disturbed DNA methylation patterns in lung fibrosis [27]. Moreover, there are some preclinical data in which authors have shown that DNMTis has the potential to reduce markers of lung fibrosis, thereby helping to improve lung function [53]. Interestingly it has been shown via preclinical models and molecular data that if two therapies such as DNMT inhibitors with histone deacetylase inhibitors (HDACis) combined then it may have beneficial effects [54]. Nevertheless, more optimization and clinical trials need to be conducted to investigate the full potential of this combined therapy to treat lung fibrosis.

Modulating Histone Modifications for Treating Lung Fibrosis

Histone modifications, including acetylation, methylation, phosphorylation, and ubiquitination, play vital roles in controlling gene expression in lung fibrosis. Dysregulated histone modifications contribute to disrupted cellular functions and abnormal gene expression profiles observed in fibrotic lungs, suggesting a potential therapeutic avenue. Histone Deacetylase Inhibitors (HDACis) inhibit histone deacetylases, promoting an open chromatin structure and enhancing accessibility to genes involved in fibrotic processes [55]. Preclinical studies demonstrate the therapeutic potential of HDACis like vorinostat and trichostatin A, which reduce fibrotic phenotypes, diminish tissue deposition, and improve lung function in pulmonary fibrosis models [56]. In lung fibrosis, histone modification or alternation can also be achieved by adjusting histone methyltransferases and demethylases by selection of inhibitors of these enzymes may further help in the optimization of histone methylation patterns which reestablish normal gene expression profiles in fibrosis [57].

Epigenetic Editing Methods in Lung Fibrosis

Genome information in lung fibrosis is one of the important assets in ruling out the role of many genes and helping in providing the role of candidate genes that may be involved in the progression of lung fibrosis. There are so many advanced high-throughput technologies such as DNA microarray, next-generation sequencing (RNA sequencing) [58], and chromatin immunoprecipitation sequencing (ChIP-seq) by which one could find out the candidate gene expression in lung fibrosis. It is recently been noticed that CRISPR-Cas9 is one of the best tools for genome editing and using this tool one can alter epigenetics, particularly, DNA methylation or histone modification patterns in many disease conditions, out of which lung fibrosis is one of them. Using the CRISPR-Cas9 method, it is also easy to minimize the gene expression patterns, which have been seen altered in lung fibrosis [57, 58]. There is a version of Cas9, which is very well now as dCas9. This version lacks catalytic activity and thus can be used with enzymes that precisely alter the DNA methylation or histone modification patterns at genes of interest [59]. There was a report published in which a lung fibrosis model was used and demethylation of candidate fibrotic genes was targeted using dCas9-fused demethylases. The results were remarkable and showed the reactivation of genes that were suppressed. Another group has proven that if dCas9 is linked to histone acetyltransferases, then the histone acetylation process in the cell can be targeted towards modulation of gene expression pattern in lung fibrosis [60]. However, these tools of genome editing are new, and therefore, lot of optimization is further to be needed before investigating its full potential in clinical trials. To fully utilize epigenetic editing as a therapeutic tool in precision medicine for lung fibrosis, these obstacles must be overcome. To overcome these challenges and advance the research toward ground-breaking therapeutic applications, cooperation between scientists, physicians, regulatory agencies, and industrial stakeholders is very much required.

CONCLUSION

Pulmonary fibrosis is one of the lung diseases, that occurs due to damage to lung tissue and thus it becomes harder and scarred, enabling lungs to work properly. Unfortunately, few medicines are there like Pirfenidone which provides short-term relief to the patient. Still, there is an urgent need for a drug against lung fibrosis that may provide long-term benefits with no side effects. Here, we have discussed the role of epigenetics in regulating lung fibrotic processes and its importance in the potential therapeutic options, and diagnostic markers. The furthermost common epigenetic modification, mainly by DNA methylation and histone modifications, non-coding RNAs was discussed as an emerging method for the treatment of lung fibrosis. Subsequently, the therapeutic potential of inhibitors like DNA methyltransferase inhibitors (DNMTis) and histone deacetylase inhibitors (HDACis) in lung fibrosis was discussed. Moreover, the potential role of the genome editing tool that is CRISPR-Cas9 was also discussed in the treatment purpose of lung fibrosis. However, there are some limitations and challenges related to these technologies, and must be optimized before their successful trials for lung fibrosis patients. By navigating the complexities of the epigenetic landscape and leveraging innovative therapeutic strategies, we can strive towards transformative clinical applications that improve patient outcomes and quality of life.

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