Interaction between long non-coding RNA and microRNA in lung diseases

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Abstract

Non-coding RNAs are a group of RNAs that cannot synthesize proteins, but are critical in the regulation of gene expression. A growing number of studies discovered that miRNAs and lncRNAs, as the two major members of the ncRNA family, play vital roles in regulating the physiological and pathological processes of lung diseases, such as pneumonia, COPD (chronic obstructive pulmonary disease), lung cancer, and asthma. These interactions are intricately linked to the the regulation of immune response, cell proliferation and apoptosis, cell differentiation and polarization, cytokine secretion, or acts as tumor suppressors or promoters. Understanding the role of ncRNAs in lung diseases might provide novel insights into disease mechanisms and potential therapeutic targets. In this review, we will go over the fundamental characteristics and functions of miRNAs and lncRNAs, their potential interaction mechanisms, then summarize the newly explorations on the role of these interactions between lncRNAs and miRNAs in various lung diseases.

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Abstract

Non-coding RNAs are a group of RNAs that cannot synthesize proteins, but are critical in the regulation of gene expression. A growing number of studies discovered that miRNAs and lncRNAs, as the two major members of the ncRNA family, play vital roles in regulating the physiological and pathological processes of lung diseases, such as pneumonia, COPD (chronic obstructive pulmonary disease), lung cancer, and asthma. These interactions are intricately linked to the the regulation of immune response, cell proliferation and apoptosis, cell differentiation and polarization, cytokine secretion, or acts as tumor suppressors or promoters. Understanding the role of ncRNAs in lung diseases might provide novel insights into disease mechanisms and potential therapeutic targets. In this review, we will go over the fundamental characteristics and functions of miRNAs and lncRNAs, their potential interaction mechanisms, then summarize the newly explorations on the role of these interactions between lncRNAs and miRNAs in various lung diseases.

Keywords

lncRNA; miRNA; RNA interaction; lung diseases

Introduction

Since non-coding RNAs (ncRNAs) without the ability to encode proteins, they were long ignored as "noise" for a long time. We have only recently realized the critical function ncRNAs play in the gene transcription and translation process. Only about 2% of human genes have protein-coding potential, the remaining 98% known as non-coding RNAs, mainly include mainly include ribosomal RNA (rRNA), transfer RNA (tRNA), ribozymes, small nuclear RNA (snRNA), small nucleolar RNA (snoRNA), microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNA (circRNAs) [1] .The newly technologies such as high-throughput sequencing (HTS) made it possible to detect RNA's structure and expression, biological functions, and interactions of RNA-RNA, RNA-DNA, and RNA-protein with high sensitivity and accuracy. To further comprehend their functions and molecular mechanisms, then establish the relationship with diseases of multiple species[2].

LncRNA and miRNA bind and interact with each other in variety ways, influencing downstream gene expression. Increasing evidences shows that RNA-RNA interactions, especially lncRNA-miRNA interactions, are crucial for gene expression in physiological and pathological processes. Furthermore, lncRNA and miRNA, which are expressed in all kinds of diseases and are involved in gene regulation, cellular metabolic process, may be ideal biomarkers or therapeutic targets in the diagnosis and treatment of cancer[3].

The regulation of immune response, cell proliferation and apoptosis, cell differentiation and polarization, and cytokine secretion are all influenced by lncRNA-miRNA interactions, which also play a significant role in the developing, advancing, and complications of lung diseases. In this review, we summarize several potential regulatory mechanisms of lncRNA-miRNA interactions: 1) lncRNA represses miRNA expression; 2) ceRNA mechanism; 3) miRNA negatively regulates lncRNA; 4) lncRNA and miRNA mutually repress each other; 5) LncRNA co-expresses with miRNA as a primary-miRNA. Based on these mechanisms, the latest studies are reviewed to reveal how lncRNA-miRNA interactions in relation to the six prevalent lung diseases: pneumonia, COPD, lung tumors, asthma, ARDS, and pulmonary fibrosis.

1. LncRNA-miRNA interactions

1.1 LncRNA

LncRNAs, longer than 200 nt, stimulate or inhibit transcription at the transcriptional level, influence mRNA splicing, editing, translation, or stability at the post-transcriptional level, and performing epigenetic regulation[2]. As reside in various cells and subcellular localizations, different lncRNAs serve diverse activities at different times. The following categories can be determined by where they are located on coding genes: 1) Intergenic (has no overlap with protein-coding genes); 2) Antisense (enriched around the promoter or terminator ends of the sense transcript); 3) Intronic (located in the area of gene coding sites); 4) Divergent lncRNA (abundanted in the vicinity of transcription start sites); 5) Pseudogenes (genes that have no potential of coding) [4]. Divergent lncRNAs, which are head-to-head overlap with the coding genes, account for about 20% of all lncRNAs. Divergent lncRNAs are strongly tied to essential growth and developmental regulatory genes. Their functions are associated with those of their neighboring coding genes, which can regulate those genes in cis and encourage the diversification of higher eukaryotic phenotypes[5]. With a countless number of lncRNA, more are continually being found and labeled, and many lncRNAs' roles have not yet been thoroughly investigated.

1.2 MicroRNA

MicroRNAs are small endogenous non-coding RNAs that are 18 to 25 nucleotides in size, with high conservation and specificity[6]. MiRNA are crucial regulators of gene expression as post-transcriptional silencing by binding and inhibiting target genes' translation, widely involved in growth development and pathological processes[7].

Intergenic miRNAs be transcribed with their own promoter independently, whereas intragenic miRNAs be transcribed together with the host gene. Long chain primary transcripts (pri-miRNAs) be transcribed and then cuts by Drosha protein complex and generates pre-miRNA, after transported to cytoplasm from

nucleus, pre-miRNA being cut and modified by Dicer enzymes to form mature miRNAs[8]. By partially complementary binding to the target gene's 3' non-coding region (3'UTR), miRISCs (miRNA-induced silencing complexes) leading to transcriptional repression of the target mRNA with no impact on mRNA stability. Completely complementary binding directly cleaves target mRNA. Besides,miRNA also could lead mRNA deadenylation, transcriptional repression or cleavage may trigger the deadenylative processes of mRNA[9]. It has been also reported that miRNAs binding to the 5'-UTR of mRNA may activate translation[10]. MiRNAs suppression and activation of target mMiRNA regulate nearly all biological functions, including cell division, proliferation, differentiation, apoptosis, and cell cycle[11].

MiRNA involved in genes regulation networks, miR-21, miR-29 family, miR-27(a/b), miR-34 in oral fluids were shown to be biomarkers in the tooth movement, modulating the process of osteoblastogenesis, osteoclastogenesis, and extra-cellular matrix conformation post-transcriptionally, and regulating the Physiological processes of orthodontic-related bone and tissue remodeling[12]. MiR-1 and miR-133, act as co-transcriptional and co-regulatory factors[13], that are highly expressed in injured myocardial tissue, encapsulated in exosomes and released into circulation, mediating the mobilization of bone marrow progenitor cells from bone marrow to the peripheral circulation and participating in the repair of myocardial ischemia[14].

1.3 The potential mechanisms of lncRNA-miRNA interaction

1.3.1 LncRNA represses miRNA expression

LncRNA bind with miRNA and suppress its expression by common binding sites, or lncRNA directly suppressing miRNA precursors or primary miRNAs, thereby lowering transcription product creation. Lnc-PFAR stems pre-miR-141 maturation by binding with pre-miR-141 in 72 Nucleotide binding domain, thus reducing miR-141 expression[15]. Rather than direct bind and interact with mature miRNA, lnc uc.173 combined with pri-miR-195 in its central stem region, destabilizing and enhancing degradation of pri-miR-195, thus inhibiting Dorsha-mediated pri-miRNA processing to pre-miRNA, and deregulate the expression of miR-195[16]. In addition, the binding of lncRNA to miRNA, or miRNA binding sponge, exerts a role in inhibiting miRNA function, while further affect the mRNA levels of miRNA downstream targets, and this mechanism of interaction by competitively binding miRNA to mRNA is known as the ceRNA mechanism.

1.3.2 CeRNA

Competitive endogenous RNA (ceRNA) reveals a novel role of RNA-RNA interaction, which has been heavily studied in recent years. At the post-transcriptional level, miRNA attaches to the miRNA response element (MRE) at the 3'-UTR end of the target gene and suppresses translation. While certain lncRNAs produce MREs as well as function as miRNA sponges, competing to other targeted mRNAs. The ceRNA mechanism refers to the competitive binding between lncRNAs and mRNAs[17]. Other RNAs, such as mRNA, pseudogenes, and circRNA also can serve in this way as ceRNA[18].

LncRNA Sox2ot from exosomes derived from highly invasive tumor cells, binding to miR-200 as ceRNA mechanism, upregulate Sox2, to induce epithelial-mesenchymal transition (EMT) and stem cell like properties in different tumor cells, plays important roles in pancreatic ductal adenocarcinoma invasion and metastasis[19]. Lnc SNHG1 promote neuroinflammation, and neuronal toxicity via different mechanisms,in the process of Alzheimer's disease, it could act as ceRNA for miR-137, targeting KREMEN1 in the human primary neuron (HPN) cells, reduce cell viability, promote cell apoptosis, decrease mitochondrial membrane potential and the protein levels of cytochrome C[20].

Whereas, there are some reports claiming that ceRNA only performs a slight role in miRNA regulation, single ceRNA is unlikely to have any biologically significant effects on the activity of miRNAs, or the expression of genes[11, 21]. Most of RBP and miRNAs regulate gene expression post-transcriptional have thousands of binding sites, the numbers of these binding sites are highly dynamic as transcription renders, only strong binding sites are likely to be altered by this crosstalk effect[22].

1.3.3 LncRNA co-expresses with miRNA as a pri-miRNA

Some miRNAs host genes can encode both lncRNA and miRNA, one of the functions of this class of lncRNAs is to act as primary miRNA, termed lnc-pri-miRNAs, able to produce miRNAs[23]. Among them, lnc LOC646329 can act as both a pri-miRNA to produce miR-29a/b1, and a transcriptional enhancer to activate neighboring oncogenes and promote Glioblastoma cell proliferation[24]. The genomic organization of lnc MIR100HG, is located on human chromosome 11 (hsa chr11),generate miR-100 and miR-125b,which co-represses several Wnt/β-catenin negative regulators,to rescue cetuximab responsiveness of cetuximab-resistant colorectal cancer and head and neck squamous cell cancer cell lines[25].

1.3.4 MiRNA negatively regulates lncRNA

TMPO antisense RNA 1 (TMPO-AS1) gene, located on chromosome 12, served as the diagnostic and prognostic marker of lung adenocarcinoma (LUAD). MiR-383-5p binding with lnc TMPO-AS1 and inhibits its expression, significantly reducing tumorigenesis and progression of LUAD[26].

MALAT1 is each individually suppressed by MiR-216a,miR-216b and miR-217. Especially, miR-216a and MALAT1's association further induced G2/M arrest and cell cycle inhibition, decreased cell viability and apoptosis in pancreatic cancer cells[27].

1.3.5 LncRNA and miRNA mutually repress each other

While lnc MIR31HG can act as a sponge to bind miR-193b, miR-193b can also directly target two binding sites on lnc MIR31HG, negatively regulates lnc MIR31HG levels, induces apoptosis and G1/S phase arrest, and reduces the cell growth of pancreatic ductal adenocarcinoma. These mutually inhibitory effects contribute to the growth of tumors[28]. A negative feedback pathway is formed between lnc MALAT1 and miR-200c-3p. On the one hand, miR-200c-3p can mediate the silencing of MALAT1, which plays a significant role in the migration and invasion of pancreatic ductal adenocarcinoma and can be used as a prognostic indicator. On the one hand, the high expression of lnc MALAT1 in pancreatic ductal adenocarcinoma inhibits the expression of miR-200c-3p[29].

See the details of the mechanism in Fig 1.

2. Functions in several lung diseases

2.1 Pneumonia

Pneumonia can be brought on by a wide range of microorganisms, including bacteria, viruses, mycoplasma, and fungus. When microorganisms invade, nonspecific immunity responds positively with the release of inflammatory factors and other immunomodulators from macrophages, which are the primary source of inflammatory factors. In the same time, macrophages directly engulf and kill microorganisms. Following this, neutrophils and other immune cells are recruited, then neutrophils perform pathogen clearance by phagocytosis of lysosomes, formation of neutrophil extracellular traps (NETs), and degranulation to release myeloperoxidase (MPO), gelatines B (MMP9), while also producing inflammatory factors and chemokines[30].Surface active proteins (SP-A, SP-D, etc.) synthesized by alveolar II epithelial cells directly inhibit microbial activity. The pulmonary immune system maintains a balance between the clearance of invading pathogens and the functional and ecological integrity.

The most common pathogens of hospital-acquired pneumonia are Enterobacteriaceae, Staphylococcus aureus, Pseudomonas aeruginosa and Acinetobacter baumannii[31]. In some cases, there may be multiple bacterial infections, concurrent bacterial pneumonia and influenza, or secondary bacterial infections after an exacerbation of a viral infection. The most common pathogen for secondary bacterial infections is Staphylococcus aureus, followed by Streptococcus pneumonia, Haemophilus influenza, and group A streptococcus[32]. About 25% of patients develop secondary bacterial infections after influenza A (H1N1) infection[33].

Influenza A virus infection stimulates IFN-β transcription, which in turn upregulates lnc-ISG20 expression. lnc-ISG20 acts as a ceRNA competing with ISG20 to bind miR-326, reducing the inhibition of ISG20 translation and negatively regulating the replication of influenza A[34]. There are also retroviruses known as

Prototype foamy virus (PFV) that cause no clinical symptoms after infection. Lnc-RP5 binding to miR-129-5p and boost its expression as a result of the infection, repressing Notch1 to increase the unique internal promoter of PFV, thus active the expression of the viral transcriptional transactivator, be critical to the replication, expression, and transportation of virus[35].

Both lnc-ANRIL and miR-125a are associated with the severity and pro-infammatory factors level of sepsis, also are high value predictive biomaker for short-term sepsis risk and 28-day mortality[36]. Additionally, lnc-ANRIL/miR-125a axis shows more efficient in the prediction of the sepsis risk, correlation with the organ damage and a series of inflammatory factors of sepsis[37]. Overexpression of lnc NKILA leads to the upregulation of miR-21, inhibition of JNK/NF-ϰB pathway, and reduces immune response and lung fibroblast apoptosis and cell viability in pediatric pneumonia[38].

Since Decemeber 2019, the rapid spread of the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) transmitted via respiratory droplets has led to a worldwide pandemic of the coronavirus disease 2019 (COVID-19)[39]. Patients who are infected may show no symptoms for a brief period of time, and rapidly developing a high fever and severe respiratory symptoms (cough, shortness of breath, etc.), along with other nonspecific symptoms including malaise, myalgia, nausea, and vomiting[40].

It has been found that miR-146a-5p, miR-21-5p and miR-142-3p are relatively lowly expressed and miR-15b-5p is highly expressed in the serum of COVID-19 patients. Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) can bind to miR-146a-5p and miR-142-3p and shows a negative correlation with both[41]. Furthermore, patients with lower miR-146a-5p expression levels responded to Tocilizumab less well [40). MALAT1 and Nuclear-enriched autosomal transcript 1 (NEAT1) expression was elevated in SARS-CoV-2-infected bronchial epithelial cells[42].

NEAT1 target miR-21 in allergic rhinitis to inhibit its anti-inflammatory effects and exacerbate the extent of the allergic inflammatory response[43]. Therefore, it is hypothesized that MALAT1 silencing miR-146a-5 and NEAT1 targeting miR-21 may serve as targets for COVID-19 therapeutic targeting.

2.2COPD

Airflow limitation with persistent respiratory symptoms and lung chronic inflammation are the main features of COPD, which is characterized by typical, prolonged dyspnea, cough and sputum, mainly due to long-term immune response brought on smoking, occupational exposure, etc.[44]. Increasing studies have shown that lncRNAs and miRNAs may be closely related to the occurrence and development of COPD, could be potential biomarkers and therapeutics[45]. As a predictor of susceptibility, NEAT1 is also associated with disease severity and inflammation level, has increased expression in the peripheral blood of COPD patients, and functions in this way by down-regulation the expression of miR-193a[46]. As a therapeutic way, RNA drugs are highly specific and safe, may be one of the ideal method of administration for COPD[44]. miR-146 affects pulmonary bronchial epithelial cells to have anti-inflammatory effects in a number of chronic lung disorders. Since lnc-PVT1 affects miR-146, its expression level can be utilized to distinguish acute exacerbation of COPD (AECOPD) patients and stable cope patients. lnc-PVT1 expression also predicting COPD susceptibility and AECOPD risk, and is positively correlated with inflammation factors and disease severity stages[47].Through RNA sequencing and Bioinformatics prediction, Qian et al. Created a miRNA-mRN-lncRNA ternary interaction network in non-smoking COPD patients and projected that miR-218-5p/miR15a-RORA-LOC101928100/LINC00861 and miR-218-5p/miR15a-TGF3-RORA-AS1 interactions play a significant role in the pathogenesis of non-smoking COPD patients[48].

Inducing oxidative stress from cigarette smoking results in severe cellular damage and an inflammatory response, which is a key pathogenic aspect of COPD. When cigarette smoke is applied to cells in vitro, it can cause cytotoxicity and an immunological response. Bronchial epithelial cells treated with smoke extraction have higher levels of lncRNA MEG3, which causes higher cell apoptosis and inflammation by sponge binding to miR-181a-2-3p [49]. Since lnc RP11-86H7.1 interacted with miR-9-5p through a ceRNA mechanism, which would lower miR-9-suppression 5p's of NFKB1 production in bronchial epithelial cells, Zhao et al. hypothesized that such ternary network may boost PM2.5 related COPD[50].

2.3 Lung cancer

Lung cancer is the leading cause of cancer-related deaths, non-small cell lung cancer (NSCLC) which has an aggressive clinical course, is the most common type of lung cancer, adenocarcinoma is the most common histologic subtype of NSCLC, and squamous cell is the second common subtype [51, 52].

MALAT1, H19, and MEG3 are highly expressed in lung cancer tissue and have been shown to be involved in all stages of lung cancer formation. They are also important markers for the diagnosis and prognosis of lung cancer. LncRNAs are crucial roles and lncRNA-miRNA interactions are the most prevalent synergistic effects in tumors [21]. MALAT1 is regarded as a predictive marker for lung adenocarcinoma and was one of the earliest genes related to lung cancer to be discovered. The majority of MALAT1 is found in nuclear speckles, where it interacts with a variety of transcription factors, chromatin modifiers, and RNA binding proteins (RBPs) to control both transcriptional and post-transcriptional gene expression[53]. Malat1 is an essential lncRNA implicated in tumor growth, invasion, and metastatic processes even though it is not necessitated for normal tissue growth and development[54]. By increasing MALAT1 stability and modifying it through m6A methylation, METTL3 promotes MALAT1 spongy binding to miR-1914-3p, which in turn promotes YAP expression and YAP-induced metastasis and invasion in NSCLC[55].

HOTAIR is linked to the formation of several tumors, and one of the mechanisms is that HOTAIR controls several downstream targets via different signaling pathways, which are linked to tumor cell motility, proliferation, angiogenesis, invasion, and drug resistance[56]. MiR-613 is downregulated by HOTAIR, that is an extremely low expression in NSCLC tissues, which facilitates NSCLC invasion and metastasis [57] and mediates NSCLC genesis. In NSCLC cells, miR-221 reduces HOTAIR expression and increases apoptosis[58]. By interacting with miR-149-5p, HOTAIR drives the emergence of cisplatin resistance in NSCLC [59]. HOTAIR also mediates miR-217/DACH1 signaling pathway regulating proliferation, migration, and invasion of lung cancer cells[60].

Other lncRNA-miRNA interactions have also been demonstrated to contribute to lung tumorigenesis. For instance, in a feedback loop formed by lnc ZEB1-AS1 and miR-409-3p/ZEB1, miR-409-3p functions as a regulatory bridge, is suppressed by lnc ZEB1-AS1 thereby upregulating ZEB1, which then binds to the lnc ZEB1-AS1 promoter regions to promote tumorigenesis[61]. Lnc GACAT1 expression is increased in NSCLC tissues and cell lines, spongiosely binds miR-422a and inactivates the YY1 transcription factor (YY1), which may be associated with poorer clinical outcomes for patients[62].

Other lncRNA-miRNA interactions mechanisms in lung cancer see in the table 1.

LncRNA	MiRNA	Mechanism	Downstream targets	Functions	Cancer type	Reference
ATB	miR-590-5p	lncRNA represses miRNA expression	NF-90	ATB upregulated in lung tissue and promote tumorigenesis and cell proliferation, migration, and Invasion	Lung Squamous Carcinoma Cell	[63]

LncRNA	MiRNA	Mechanism	Downstream targets	Functions	Cancer type	Reference
CHRF	miR-489	lncRNA represses miRNA expression	Myd88	lncRNA CHRF modulate miR-489/Myd88 axis to inhibit cell proliferation, Migration, Invasion, Apoptosis	NSCLC	[64]
CCAT1	miR-218	lncRNA represses miRNA expression	BMI-1	lncRNA CCAT1 downregulate miR-218 then inhibit BMI-1 to promotes anti-apoptosis and cell proliferation	NSCLC	[65]
DLEU2	miR-30c-5p	ceRNA	SOX9	lncRNA DLEU2 downregulate miR-30c-5p and promote SOX9, contribute to tumorigenesis and metastasis, shorter overall survival	NSCLC	[66]

LncRNA	MiRNA	Mechanism	Downstream targets	Functions	Cancer type	Reference
MBNL1-AS1	miR-301b-3p	ceRNA	TGFBR2	lncRNA MBNL1-AS1 positively regulated TGFBR2 by competitively binding to miR-301b-3p, promote proliferation, migration, invasion, drug resistance, and sphere formation of cancer stem cell	NSCLC	[67]
LINC00240	miR-7-5p	ceRNA	EGFR	LncRNA LINC00240 suppresses invasion and migration by sponging miR-7-5p and induced the overexpression of EGFR	NSCLC	[68]
XIST	miR-335	ceRNA	SOD2	XIST facilitated NSCLC progression by miR-335/SOD2/ROS signal pathway inhibited pyroptotic cell death	NSCLC	[69]
LINC00662	miR-320d	ceRNA	E2F1	LINC00662 promotes cancer progress by miR-320d/E2F1 axis	NSCLC	[70]

LncRNA	MiRNA	Mechanism	Downstream targets	Functions	Cancer type	Reference
MEG3	miR-7-5p	ceRNA	BRCA1	MEG3 increases apoptosis of lung cancer cells by competitive binding to microRNA-7-5p reducing the BRCA1 expression.	NSCLC	[71]
LINC01436	miR-30a-3p	ceRNA	EPAS1	LINC01436 promotes lung cancer cell growth, migration, and invasion	NSCLC	[72]
CASC2	miR-21	lncRNA represses miRNA expression	p53	CASC2 suppresses cell proliferation and enhances apoptosis.	LUAD	[73]
H19	miR-107	ceRNA	NF1	H19 increases the proliferative and migratory abilities of cancer cells	NSCLC	[74]
H19	miR-196b	ceRNA	LIN28B	H19 accelerates cell proliferation in lung cancer	lung cancer	[75]
LINC00857	miR-1179	ceRNA	SPAG5	LINC00857 promoted cell growth and glycolysis and repressed apoptosis	LUAD	[76]

LncRNA	MiRNA	Mechanism	Downstream targets	Functions	Cancer type	Reference
NNT-AS1	miR-129-5p	ceRNA	-	NNT-AS1 increases lung cancer cells proliferation and invasion ability	NSCLC	[77]
SNHG16	miR-520	ceRNA	VEGF	SNHG16 drives proliferation, migration, and invasion of lung cancer cell	NSCLC	[78]
UCA1	miR-383	ceRNA	VEGFA	UCA1 increases cell proliferation, migration and invasion	LUAD	[79]
PGM5P4-AS1	miR-1275	ceRNA	LZTS3	PGM5P4-AS1 inhibiteS lung cancer cell proliferation, migration, and invasion activities	lung cancer	[80]
1308	miR-124	ceRNA	ADAM15	facilitates NSCLC cell proliferation and invasion	NSCLC	[81]
DLGAP1-AS1	miR-193a-5p	ceRNA	DTL	exhibits oncogenic properties	NSCLC	[82]
GAS5	miR-21	ceRNA	PTEN	increases the radiosensitivity and promotes the IR-induced cell apoptosis	NSCLC	[83]
PVT1-5	miR-126	ceRNA	SLC7A5	promotes cell proliferation	lung cancer	[84]

LncRNA	MiRNA	Mechanism	Downstream targets	Functions	Cancer type	Reference
SNHG3	miR-1343-3p	ceRNA	NFIX	promotes the development of non-small cell lung cancer	NSCLC	[85]
SNHG4	miR-let-7e	ceRNA	KDM3A	promotes cell viability, colony formation, invasion, migration, and cycle progression while reducing apoptosis	NSCLC	[86]
SNHG1	miR-145-5p	ceRNA	MTDH	promotes non-small cell lung cancer progression	NSCLC	[87]
LOC146880	miR-539-5p	miRNA negatively regulates lncRNA	ENO1	declines phosphory-lation of an oncogene, ENO1, and then reduces cell proliferation and tumor progression	NSCLC	[88]

Table 1. Other lncRNA-miRNA interaction mechanisms in lung cancer

Abbreviation: NSCLC, non-small cell lung cancer; LUAD, Lung adenocarcinoma.

2.4 Asthma

Asthma is one of the most prevalent chronic inflammatory diseases, typically characterized by airway hyper-responsiveness and airway obstruction, and nonspecific airway symptoms caused by specific triggers (such as allergens, environmental factors, infections, etc.). Airway remodeling, including thickening of the airway wall and narrowing of the airway, can occur in younger children as a result of epithelial injury, cilia failure, cupular cell proliferation, fibroblasts, and growth of airway smooth muscle cells[89]. For now, there are approximately 300 million asthma patients worldwide[90]. Over the last 40 years, there has been a significant surge on the prevalence, morbidity and mortality associated with asthma among children[91].

Through its association with miR-124, lnc-NEAT1 triggers the release of a number of inflammatory cytokines, and it is linked to a high risk of severe asthma exacerbations [92]. Besides this, lnc PVT1 suppresses the expression of miR-149, increases inflammation in small airway epithelial cells, and impairs cellular de-

fense barrier function[93]. Asthma-related lung inflammation is mediated by CD4+ T cells, and asthma development is facilitated by enhanced T cell differentiation of Th2 cells. Asthma-induced lung inflammation is amplified as lnc MALAT1 competitively binds miR-155 with CTLA-4 through a ceRNA mechanism. This can boost CTLA-4 expression, which in turn causes up- and down-regulation of the essential Th1/Th2 transcription regulators T-bet and GATA3[94].

Airway smooth muscle cells (ASM) are the primary effector cells in asthma, and several studies have revealed that ASM cells proliferate in asthma patients and promote a more contractile ASM phenotype in response to inflammatory factor stimulation[95]. The upstream lnc NEAT1 was identified to modulate SLC26A2 expression by targeting miR-9-5p, enhance ASM cell proliferation, migration, contraction, and boost inflammation in child asthma patients[96].

Platelet-derived growth factor BB (PDGF-BB) stimulates Malat1 expression in airway smooth muscle cells, Malat1 interacts with miR-150 by a ceRNA mechanism, significantly enhances the essential translation initiation factor, eIF4E, and Akt signaling, promotes airway smooth muscle cells proliferation and migration, airway remodeling in asthma[97]. Meanwhile, there are studies demonstrated that lnc GAS5 acts on miR-10a/BDNF axis[98], lnc PVT1 acts on miR-590-5p/FSTL1 axis[99], lnc Malat1 acts on miR-150-eIF4E/AKT axis[100] influencing ASM cell proliferation and migration in asthma.

2.5 ARDS

ARDS was known as non-cardiogenic respiratory failure with severely impaired pulmonary function, hypoxemia, and decreased pulmonary compliance, with around 30 million patients every year[101] and mortality rate ranging from 34.9% to 46.1% depending on the severity[102]. ARDS is caused by pulmonary infections (bacterial, viral, etc.), other significant infections (skin, genitourinary system, etc.), burns, particularly smoke inhalation, and all kinds of traumas[103]. There are no specialized treatment options, and therapy is still reliant on lung-protective mechanical ventilation.

When microorganisms, irritant mediators, and so on infiltrate the alveolar barrier, macrophages polarize from resident alveolar macrophages to the M1 phenotype at an early stage in response to Toll-like receptors (TLR) induced by infection, releasing pro-inflammatory factors such as IL-1, IL-6, and TNF-α, which are the first hurdle of lung immune response[104], while pro-inflammatory Inflammation is exacerbated by further activation and release of pro-inflammatory factors, chemokines, adhesion molecules, and so on. The main mechanism of ARDS is assumed to be the acute, widespread lung inflammation caused by this overwhelming immune response [105].

A large number of miRNAs, such as miR-146, miR-155, miR-221, and miR-222, have been noted to be stimulated upon TLR signaling activation, and lncRNAs such as Mirt2, THRIL, MALAT1, and lincRNA-21 are also altered upon TLR activation and negatively regulate TLR signaling as well as suppress pro-inflammatory factor expression[106]. MALAT1 is highly expressed in inflammation-activated macrophages, interacts with NF-ϰB, inhibits TLR signaling, and lowers TNF-α, IL-6 and other inflammatory factors [107]. HOTAIR affects the miR-30a-5p/PDE7A axis in LPS-induced ARDS, increases the release of inflammatory factors, and exacerbates the pulmonary inflammatory response[108].

2.6 pulmonary fibrosis

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive interstitial lung disease mainly occurs in the elderly. It has a poor prognosis, a high mortality rate, and prone to acute exacerbation to respiratory failure[109]. Its etiology is still unknown, however, is frequently associated with smoking, occupational exposure, air pollution, and infection. Damage and repair of alveolar epithelial cells owing to numerous causes, activation of fibroblasts, stimulation of fibropathic proliferation, recruitment and proliferation of immune cells such as alveolar macrophages and lymphocytes, and modulation of the fibrotic response [110], gradual destruction of the normal structure of the lung, and progressive decompensation of lung function IPF can't be reversed or stopped once it starts, although a number of medications now used to treat it can only slow its advancement[111].

The epithelial-mesenchymal transition (EMT) is critical in the advancement of pulmonary fibrosis since epithelial cells able to de-differentiate then differentiate into mesenchymal cells, which continually produce and accumulate extracellular matrix, directly tied to signaling pathways such as TGF-1, Smad, and ERK/MAP [112]. Silicosis is caused by long-term silica inhalation and deposition in the lungs, which leads to diffuse pulmonary fibrosis. Macrophages are prompted to release TGF-1, which causes lnc ATB expression in epithelial cells and binds to miR-200c to increase ZEB1 expression in silica-induced silicosis pulmonary fibrosis [113]. In addition, miR-29b-2-5p and miR-34c-3p are targets for sponging binding downstream of lnc ATB, upregulating the expression of MEKK2 and NOTCH2, enabling lnc ATB to contribute to the acceleration of the EMT process [114]. Lung epithelial cells express more proliferation and EMT-related genes when lnc NEAT1 interacts with miR-29c [115]. lnc RFAL binds to miR-18a and activates fibroblasts via CTGF to accelerate the process of lung fibrosis [116], lnc RFAL also suppresses miR-26a expression, therefore inhibiting miR-26a's anti-fibrotic action. A mutually inhibitory feedback loop established between miR-26a and Smad2, leads lnc PFRL to increase fibroblast proliferation and transform into myofibroblast [117].

Liu et al. reported that in silica-induced lung fibrosis in mice fibroblasts, the overexpression of lnc PCAT29 elevated miR-221 expression, inhibited TGF-β1 in lung fibroblasts, and slowed the lung fibrosis process through the RASAL1/ERK1/2 signaling pathway [118].Through the miR-326/SP1 axis, lnc SNHG1 enhances fibroblast migration, invasion, and fibrogenic molecule production [119], whereas lnc SHNG6 promotes fibroblast activation and collagen accumulation via the miR-26a-5p/TGF-1-smads axis, inducing lung fibrosis in mice [120].

3.Discussion and Prospect

Lung illnesses frequently do not occur in isolation; instead, they may develop in combination with other systemic diseases, or numerous lung diseases may occur simultaneously, or due to a causative factor causes the disease to appear in diverse processes with varying clinical symptoms and disease types. Microorganisms, for example, might cause pneumonia at an early stage, but severe pneumonia may cause ARDS or even a systemic inflammatory response syndrome, which could lead to pulmonary fibrosis in a long term, pulmonary fibrosis increases the risk of lung cancer by 7% to 20%[121]. This review addresses the results and developments of lncRNA-miRNA interactions in the development, prevention, and therapy of various common and thoroughly researched lung diseases. Some star lncRNA molecules have been extensively studied in a variety of diseases. MALAT1 and NEAT1, which are involved in acute and chronic inflammation of numerous causes of lung, as well as MALAT1 and HOTAIR, which are expressed in several tumors including lung cancer.

We further noticed that research into the mechanism of lncRNA-miRNA interactions in lung diseases is more focused on the ceRNA mechanism, in which lncRNA sponges binding miRNAs, suppresses miRNA binding, and silences downstream mRNA translation. Finding potential biomarkers for disease diagnosis, degree, prognosis, or targets for therapy required an understanding of the mechanism of lung disease formation and the role played by ncRNAs in the mechanism of cure. All of that is accomplished by constructing the lncRNA-miRNA action network. However, the involvement of lncRNA-miRNA interactions in lung diseases is a sophisticated network of inter-crosstalk among innumerable ncRNAs, the roles and processes of which are yet unclear.

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Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Author Contributions

All authors contributed to the study conception and design. Material preparation by Liangliang Shi and Guochang Chen, the table was edited by Xiaoxiao Liu. The first draft of the manuscript was written by Jiaqi Li, reviewed and edited by Shengyu Huang, Funding acquisition by Mingzhuo Liu, Supervision by Guanghua Guo. All authors read and approved the final manuscript.

Ethics approval

This is a review and no ethical approval is required.

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