Non-coding RNA Research 9 (2024) 1111–1119

Contents lists available at ScienceDirect

Non-coding RNA Research

journal homepage: www.keaipublishing.com/en/journals/non-coding-rna-research

Review Article

Noncoding RNAs in chronic obstructive pulmonary disease: From pathogenesis to therapeutic targets

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ARTICLE INFO

Keywords:
COPD
miRNA
lncRNA
circRNA

ABSTRACT

Chronic obstructive pulmonary disease (COPD) is the most prevalent chronic respiratory disorder that is becoming the leading cause of morbidity and mortality on a global scale. There is an unmet need to investigate the underlying pathophysiological mechanisms and unlock novel therapeutic avenues for COPD. Recent research has shed light on the significant roles played by diverse noncoding RNAs (ncRNAs), including microRNAs (miRNAs), long noncoding RNAs (lncRNAs), and circular RNAs (circRNAs), in orchestrating the development and progression of COPD. This review provides an overview of the regulatory roles of ncRNAs in COPD, elucidating their underlying mechanisms, and illuminating the potential prospects of RNA-based therapeutics in the management of COPD.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is defined as a heterogeneous lung condition characterized by chronic respiratory symptoms, including dyspnea, cough, and sputum production, that cause persistent airflow obstruction [1]. It is considered one of the most prevalent chronic respiratory disorders worldwide, with an estimated prevalence of 10.3 %, corresponding to approximately 391.9 million individuals [2]. Furthermore, as of 2019, COPD has become the third leading cause of death worldwide [2]. The primary pathological characteristic of COPD is a persistent and atypical inflammatory reaction occurring in the lungs, leading to airway and alveolar changes, as evidenced by the presence of small airway disease and emphysema [3]. In individuals diagnosed with COPD, the emergence of pulmonary hypertension is linked to a decline in clinical status, deterioration in gas exchange, and heightened mortality rates [4]. Although it is widely accepted that smoking, outdoor and indoor air pollution, childhood respiratory infections, and genetic abnormalities are major risk factors in the pathogenesis and development of COPD, the understanding of the pathophysiology of COPD remains incomplete [2]. Consequently, there is a pressing need to investigate the pathophysiological mechanisms of COPD and therefore identify novel therapeutic targets and strategies.

Recent studies have linked a variety of noncoding RNAs (ncRNAs), including microRNAs (miRNAs), long noncoding RNAs (lncRNAs), and circular RNAs (circRNAs) to the occurrence and development of COPD [5]. Some of these ncRNAs have undergone functional characterization, revealing their potential for early diagnosis and therapeutic intervention in COPD. This comprehensive review aims to present the latest advancements in the field of COPD-associated ncRNAs and explore their prospective clinical applications.

2. MicroRNAs in COPD

MicroRNAs are a subset of small noncoding RNAs, typically spanning 21–25 nucleotides, which primarily modulate gene expression at the post-transcriptional level. The dysregulation of a series of miRNAs has been linked to the pathogenesis of COPD and other respiratory disorders [6,7]. Moreover, much research efforts have been dedicated to investigating the functional mechanisms of specific miRNAs in the progression and development of COPD (Table 1, Fig. 1).

2.1. MicrRNAs target airway remodeling

Airway remodeling is a crucial factor contributing to progressive

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https://doi.org/10.1016/j.ncrna.2024.06.005
Received 25 December 2023; Received in revised form 9 May 2024; Accepted 4 June 2024
Available online 4 June 2024

airway limitation in individuals with COPD [8]. Exposure to cigarette smoke (CS) has been shown to reduce levels of let-7 in bronchial epithelial cells, leading to increased secretion of interleukin 6 (IL-6) and subsequent differentiation of fibroblasts into myofibroblasts [9]. The suppression of miR-30 has been observed in cadmium-induced COPD [10]. This microRNA was found to inhibit the expression of SNAIL, a master regulator of epithelial-mesenchymal transition (EMT) in lung epithelial cells [11]. Notably, cadmium is a known lung carcinogen, and the cadmium-induced downregulation of miR-30 and consequential upregulation of SNAIL may contribute to the development of cadmium-associated lung cancer as well [11].

2.2. MicroRNAs target vascular remodeling

Pulmonary vascular remodeling is another prominent characteristic of COPD and is widely recognized as a key factor in the development of pulmonary hypertension [12]. Nevertheless, the precise molecular mechanisms responsible for these vascular alterations remain incompletely elucidated. Alternations in miRNA expression profiles in individuals with COPD were analyzed by several studies [13,14].

Due to the negative prognosis associated with skeletal muscle dysfunction in individuals with COPD, there has been a particular focus on muscle-specific microRNAs (myo-miRNAs), known to be involved in myogenesis and differentiation, in COPD research. Several preliminary studies have identified significant dysregulations of myo-miRNAs, such as miR-1, miR-133, and miR-206, in COPD patients [14–16]. Among them, miR-206 consistently exhibited upregulation in COPD patients' plasma and lung tissue (Table 1). According to a recent investigation conducted on human pulmonary microvascular endothelial cells (HPMECs), it was found that miR-206 could directly target Notch receptor 3 (NOTCH3) and vascular endothelial growth factor A (VEGFA), both of which play crucial roles in vascular remodeling [17]. Correspondingly, the introduction of antagomir against miR-206 to HPMECs resulted in elevated expression levels of NOTCH3 and VEGFA, thereby impeding the HPMEC apoptosis induced by cigarette smoke extract (CSE) [17].

Significant decreases in the expression levels of both miR-126 and miR-197 were observed in the lung tissue of patients with COPD. MiR-126, previously identified as a key regulator of endothelial cell differentiation, is believed to play a role in vascular remodeling in small pulmonary arteries and lung microvasculature by modulating the expression of ADAM9 (a disintegrin and a metalloprotease 9) [18]. Additionally, the expression level of miR-197 exhibited a strong negative correlation with the severity of airflow obstruction and the extent of vascular remodeling. In pulmonary arteries, miR-197 appears to mitigate aberrant vascular remodeling, potentially through the inhibition of a transcription factor E2F1 [19].

2.3. MicroRNAs target inflammation

Pulmonary inflammation is a common feature of COPD and various other respiratory diseases. Consequently, dysregulation of numerous inflammation-associated microRNAs is frequently observed across different respiratory disorders [20].

The microRNA miR-181 plays a role in modulating inflammatory cytokine levels through its direct target CCN1. Decreased expression of miR-181 in bronchial epithelial cells has been linked to heightened inflammatory responses, increased reactive oxygen species production, and the progression of COPD [21]. Interestingly, inflammatory cytokines could induce the expression of various miRNAs in return. For instance, the upregulation of miR-223, which regulates HDAC2 expression and activity in pulmonary cells, has been observed in COPD mouse models following stimulation with interleukin-1β and tumor necrosis factor-α [22].

In individuals with COPD, miR-218 expression is decreased in both bronchial epithelial cells and serum samples. In non-COPD bronchial epithelial cells, miR-218 is responsible for binding to the 3′UTR region of tumor necrosis factor receptor 1 (TNFR1) mRNA to inhibit the unwanted activation of NF-κB activation and the upregulation of interleukins [23]. Similarly, miR-27 targets the 3′UTR sequence of peroxisome proliferator-activated receptor γ (PPARγ), leading to the suppression of its activation, thereby preventing the induction of pulmonary inflammation and activation of alveolar macrophages in the development of COPD [24].

Levels of miR-3202 in blood samples exhibited a reduction among individuals with COPD, and further displayed a negative association with COPD exacerbation, indicating a potential protective role of miR-3202 in COPD patients, particularly those who smoke [25]. Subsequent investigations suggest that miR-3202 may facilitate the activation of the FAS signaling pathway by inhibiting FAIM2 (Fas apoptotic inhibitory molecule 2) expression in T-lymphocytes [25,26].

Conversely, miR-195 was found to be significantly elevated in the

Table 1
Functional microRNAs validated in COPD model.

miRNA	Dysregulation in Patients	Target Gene	Targeted Pharmacological Actions	COPD models	Ref.
miR223	Increased in lung tissue	HDAC2	Inflammation	CS + mouse	[22]
miR181	Decreased in lung tissue	CCN1	Inflammation	CSE + HBEC; CS + C57BL/6 mouse	[21]
miR218	Increased in serum and lung tissue	TNFR1	Inflammation	CSE + HBEC	[23]
miR27		PPARγ	Inflammation	CS + C57BL/6 mouse	[24]
miR195	Increased in lung tissue	PHLPP2	Inflammation	CSE + BEAS-2B; CS + C57BL/6J mouse	[27]
miR3202	Decreased in plasma by smoking	FAIM2	Inflammation	CSE + HBEC; CS + SD rat	[25, 26]
miR197	Decreased in lung tissue	E2F1	Vascular remodeling	Primary SMC	[19]
miR21	Increased in serum and lung tissue	pVHL; SATB1	Airway remodeling; inflammation	CSE + HBEC + MRC-5; CS + BALB/c mouse	[41, 42]
miR206	Increased in plasma and lung tissue	Notch3; VEGFA	Vascular remodeling	CSE + HPMECs	[17]
miR145	Decreased in lung tissue by smoking	CFTR; SLC26A9; KLF5	Mocociliary clearance; inflammation	CSE + BEAS-2B; CS + non-CF A/J mouse; CSE + HBEC	[36, 37]
miR30	Decreased in blood by cadmium exposure	SNAIL	Epithelial-mesenchymal transition	$CdCl_2$+ BEAS-2B	[10, 11]
miR155	Increased in lung tissue by smoking		Inflammation	CS + C57BL/6 mouse	[29]
let-7	Decreased in lung tissue	IL-6	Myofibroblast differentiation	CSE + HBEC + MRC-5; CS + C57BL/6 mouse	[9]
miR-34	Increased in lung tissue	SIRT1 SIRT6	Senescence	Primary HBEC	[31]
miR-570	Increased in lung tissue	SIRT1	Senescence	Primary SAEC	[32]
miR126	Decreased in lung tissue	ADAM9	Vascular remodeling	Primary HLMVEC	[18]

Abbreviations: CS, cigarette smoke; CSE, cigarette smoke extract; EMT, epithelial-to-mesenchymal transition; HBEC, human biliary epithelial cell; HLMVEC, human lung microvascular epithelial cell; HPMEC, human pulmonary microvascular endothelial cell; SAEC, small airway epithelial cell; SMC, smooth muscle cell.

lung tissue of COPD patients. Mechanistically, miR-195 enhanced AKT phosphorylation by suppressing PHLPP2 (PH Domain And Leucine Rich Repeat Protein Phosphatase 2) expression [27]. MiR-155, a well-known modulator of the immune response, was also upregulated in COPD patients [28,29]. More importantly, its expression level is strongly associated with lung function parameters of airflow limitation and diffusing capacity in patients with COPD, with the highest expression observed in end-stage COPD [28]. In a mouse model, removing miR-155 significantly reduces elastase-induced emphysema and changes in lung function, indicating its critical involvement in pulmonary inflammation and the development of COPD [29]. However, the specific molecular mechanisms underlying these effects remain unclear.

2.4. MicroRNAs target senescence

Cellular senescence is also recognized as a significant contributing factor to COPD [30]. The expression of miR-34 was found to be elevated in the lung tissues of COPD patients and was found to be correlated with the expression of senescence markers. Further investigation into the underlying mechanism revealed that miR-34 plays a crucial role in downregulating sirtuin-1 and -6 (SIRT1 and SIRT6) in bronchial epithelial cells, and inhibiting this microRNA could reverse cell cycle arrest and reduce markers of senescence [31]. The modulation of SIRT1 level by miR-570 has also been observed in individuals with COPD, with the upregulation of miR-570 being activated by p38 mitogen-activated protein kinase [32]. It is noteworthy that these miRNAs have been shown to regulate senescence in various cell types, hinting that the release and circulation of these miRNAs may provide insight into the pathogenesis of other chronic lung diseases and comorbidities associated with COPD.

Furthermore, several key miRNAs were found to participate in the progression of COPD through multiple pathways (Table 1). One example is miR-145, an established regulator in the TGF-β signaling pathway, which has been considered a promising miRNA-based therapeutic agent in breast cancer, colon cancer, and prostate cancer [33–35]. In the context of COPD models, on the one hand, miR-145 is essential for protecting airway epithelial cells against CSE-induced apoptosis and inflammation by targeting KLF5 (Krüppel-like factor 5) [36]. On the other hand, upregulation of miR-145 has been observed to suppress the expression of CFTR (cystic fibrosis transmembrane conductance regulator) and its modifier SLC26A9 (Solute carrier family 26 member 9), both of which play crucial roles in the primary innate defense of mucociliary clearance [37]. Another intriguing example is miR-21, a non-specific pro-metastatic factor in various cancers, exhibiting promising therapeutic potential in cholangiocarcinoma, colorectal cancer, and ovarian cancer [38–40]. In COPD patients, exosomal miR-21 derived from bronchial epithelial cells regulates myofibroblast differentiation via the pVHL (von Hippel-Lindau protein)/HIF1α (hypoxia-inducible factor 1α) axis. Simultaneously, miR-21 in lung tissue mediates the proliferation of airway macrophages, neutrophils, and lymphocytes via the SATB1 (special AT-rich sequence–binding protein 1)/S100A9 (S100 calcium binding protein A9)/NF-κB axis. In both scenarios, the utilization of small interfering RNA (siRNA) to target miR-21 demonstrated enhanced lung function, suggesting its potential as a promising therapeutic target for COPD [41,42].

3. Long noncoding RNAs in COPD

LncRNAs are defined as noncoding transcripts that exceed 200 nucleotides in length [43]. Initial investigations utilizing high-throughput RNA sequencing have revealed hundreds of lncRNAs to be associated with the development of COPD [44,45]. However, only recently have some of these lncRNAs begun to be functionally characterized [46–48] (Table 2, Fig. 1).

3.1. LncRNAs regulate RNA stability

The majority of these lncRNAs exert their effects by modulating local gene expression. For example, IL6-AS1, which is upregulated in the lung tissue of COPD patients, is the antisense transcript of interleukin 6. Through promoting IL-6 gene transcription and stabilizing IL-6 mRNA, IL6-AS1 enhances IL-6 production and inflammation in COPD [49].

Another lncRNA, LASI, is located on the antisense strand of the important inflammatory factor ICAM-1 (intercellular adhesion molecule

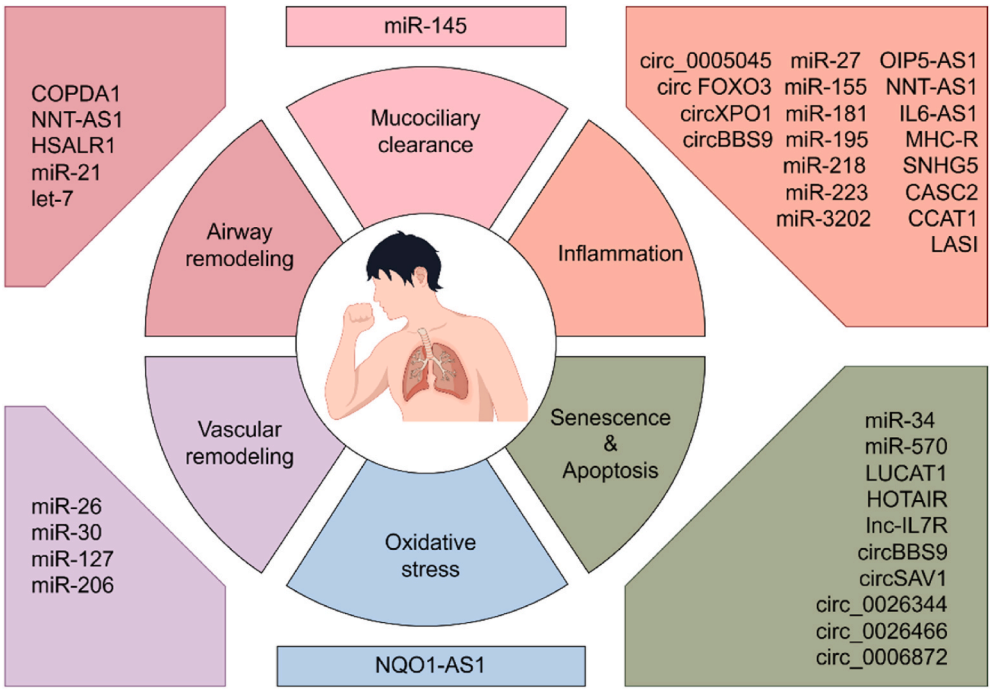

Fig. 1. Noncoding RNAs participate in COPD pathogenesis. Functional miRNAs, lncRNAs, and circRNAs have been validated in COPD models to participate in inflammation, mucociliary clearance, airway and vascular remodeling, oxidative stress response, and cell apoptosis.

Table 2
Functional lncRNAs validated in COPD models.

lncRNA	Dysregulation in Patients	Target Gene	Targeted Pharmacological Actions	COPD models	Ref.
COPDA1	Increased in lung tissue	MS4A1	Airway remodeling	HBSMC	[55]
SNHG5	Decreased in lung tissue	miR132/PTEN	Inflammation	CSE+16HBE	[58]
NNT-AS1	Increased in lung tissue	miR582-5p/FBXO11	Airway remodeling; inflammation	CSE+16HBE	[62]
CASC2	Decreased in serum	miR18a-5p/IGF1	Inflammation	CSE+16HBE	[57]
Nqo1-AS1	Increased in lung tissue and PBMC	Nqo1	Oxidative stress	CSE + MLE12; CS + C57BL/6J mouse	[52]
LUCAT1	Increased in serum	miR181a-5p/Wnt/β-catenin	Pulmonary cell proliferation and apoptosis	CSE+16HBE	[60]
IL6-AS1	Increased in lung tissue	IL-6	Inflammation	CSE/LPS/PM + HBF/HFL1	[49]
OIP5-AS1	Increased in serum	miR410-3p/IL-13	Inflammation	CSE+16HBE	[59]
LASI	Increased in lung tissue	ICAM-1	Mucus hyperexpression; inflammation	CSE + HBEC; CS + macaque	[50]
CCAT1	Increased in lung tissue	miR152-3p/ERK	Inflammation	CSE + HBE	[61]
HOTAIR	Increased in lung tissue	DNMMT1/Bcl-2	Pulmonary cell apoptosis	CSE + HPVEC; CS + C57BL/6J mouse	[54]
MHC-R			Immune response	PM + SD rat	[64]
Lnc-IL7R	Decreased in serum	EZH2/p21	Pulmonary cell apoptosis	PM + HSAEpC	[65]
HSALR1	Increased in lung tissue	HSP90AB1/pAKT	Airway remodeling	CS + C57BL/6J mouse	[47]

Abbreviations: CS, cigarette smoke; CSE, cigarette smoke extract; HBEC, human biliary epithelial cell; HBF, human bronchial fibroblast; HBSMC, human bronchial smooth muscle cell; HPMEC, human pulmonary microvascular endothelial cell; HPVEC, human pulmonary vascular endothelial cell; HSAEpC, human small airway epithelial cell; LPS, lipopolysaccharide; PM, particulate matter.

1) [50]. In COPD patients, the expression of LASI in airway epithelial cells is upregulated and positively correlated with the severity of the disease [48]. Furthermore, LASI expression induced by cigarette smoke in both human bronchial epithelial cells and the cynomolgus macaque model is positively correlated with the secretory mucin MUC5AC and airway the expression of inflammatory factors ICAM-1 and IL-6. Accordingly, the knockdown of LASI using siRNA resulted in a substantial decrease in the levels of MUC5AC (mucin 5AC), ICAM-1, and IL-6, indicating its modulatory functions in airway mucus hyperexpression and inflammatory responses [48].

NQO1-AS1 is the antisense transcript that is positioned in a tail-to-tail orientation with the NAD(P)H quinone oxidoreductase coding gene NQO1. As one of the most crucial quinone reductases, NQO1 has well-established roles in safeguarding cells against CS-induced oxidative stress and obstructive bronchitis [51]. By forming a pairing with the 3' UTR of NQO1, NQO1-AS1 serves to stabilize NQO1 mRNA and subsequently enhance NQO1 expression, thereby mitigating the CS-induced oxidative stress [52].

3.2. LncRNAs regulate transcription

HOTAIR, a well-known regulator of epithelial cell plasticity, has been implicated in facilitating the EMT in various cancer types [46]. Recently, the upregulation of HOTAIR was also observed in the lung tissue of COPD patients [53,54]. In both CS-treated mouse models and human pulmonary vascular endothelial cells, HOTAIR targets DNMT1 (DNA methyltransferase enzyme 1) to mediate the hypermethylation of the BCL-2 (B-cell lymphoma-2) promoter, thereby promoting endothelial cell apoptosis [54]. Accordingly, knocking down HOTAIR can attenuate pulmonary cell apoptosis and emphysema in CS-treated mice [54]. Another lncRNA, COPDA1, was identified to coexpress with MS4A1 (membrane-spanning 4-domains A1) in bronchial smooth muscle cells. Their upregulation was proved to be associated with the undesirable proliferation of smooth cells and airway remodeling, although the specific signaling pathways implicated in the process have not been fully elucidated [55].

3.3. LncRNAs act as protein scaffolds

Additionally, HSALR1 lncRNA not only exhibits a substantial increase in lung tissue of COPD patients but also demonstrates a robust correlation with TGF-β1 expression, a known contributor to COPD progression [56]. Under the stimulation of TGF-β1, SMAD3 (SMAD family member 3) could directly bind to the promoter of HSALR1, thereby triggering its upregulation. As a result, HSALR1 serves as a scaffold to stabilize the HSP90AB1 (heat shock protein 90AB1)-AKT complex and promote AKT phosphorylation [47]. Experiment results obtained from both human lung fibroblast cells and mice models have demonstrated that the SMAD3/HSALR1/AKT axis plays a role in promoting cell proliferation and airway remodeling during the progression of COPD [47].

3.4. LncRNAs act as miRNA sponges

The expression levels of lncRNA CASC2 (cancer susceptibility candidate 2) were found to be significantly decreased in COPD patients, particularly those classified in the severe group (GOLD stage III). CASC2 acts as a competing endogenous RNA (ceRNA) for miR-18a-5p, influencing bronchial epithelial cell apoptosis and inflammation through the miR-18/IGF1 (insulin-like growth factor 1) axis [57]. Another lncRNA SNHG5 (small nucleolar RNA host gene 5) was also observed to be downregulated in COPD lung tissues and exhibited a positive correlation with FEV1 (forced expiratory volume in 1 s), a marker of COPD severity. LncRNA SNHG5 functions as a ceRNA for miR-132, leading to increased expression of PTEN and ultimately promoting COPD exacerbation [58].

Several other lncRNAs were found to be significantly upregulated in patients with COPD. Among them, OIP5-AS1 (Opa interacting protein 5-antisense RNA 1) was found to enhance cell apoptosis and pulmonary inflammation by targeting the miR-410-3p/IL-13 axis [59]. LncRNA LUCAT1 (lung cancer-associated transcript 1) was upregulated in serum samples from COPD patients and was shown to modulate COPD progression through the Wnt/β-catenin pathway by acting as a sponge for miR-181a-5p [60]. Whereas, CCAT1 was highly upregulated in lung tissues of COPD patients and was found to promote inflammation by sponging miR-152-3p to activate the ERK signaling pathway [61]. The upregulation of NNT-AS1 was CSE-dependent. Its upregulation leads to the positive regulation of FBXO11 (F-Box protein 11) through the sponging of miR-582-5p, which in turn contributes to the promotion of apoptosis, inflammation, and airway remodeling in the context of COPD progression [62].

It is worth noting that, in addition to cigarette smoking, the global initiative for chronic obstructive lung disease (GOLD) guideline has listed air pollution as one of the major risk factors for COPD as well [1]. It was reported that the prevalence of COPD is projected to increase by approximately 1.5 times for every 5 $\mu g/m^3$ increase in exposure to fine particulate matter ($PM_{2.5}$) [63]. Therefore, in addition to those CS-induced COPD models, recent research has begun to utilize PM-induced COPD models. In a rat model exposed to PM, the lncRNA MHC-R exhibited drastic upregulation and likely participated in the pathogenesis of COPD through the regulation of immune activities in dendritic cells [64]. Furthermore, the level of another lncRNA, lnc-IL7R, was found to be decreased in the serum of COPD patients and displayed a

correlation with PM exposure. By recruiting EZH2 (enhancer of zeste homolog 2) to the p21 promoter, lnc-IL7R was able to effectively mitigate PM-induced cell apoptosis and senescence [65].

4. Circular RNAs in COPD

CircRNAs, characterized by their distinct circularized conformations, have emerged as pivotal regulators in a wide range of diseases [66,67]. While recent research advances revealed the dysregulation of certain circRNAs in COPD, only a handful of them have been subjected to functional characterization [5,68,69] (Fig. 2, Table 3).

4.1. CircRNAs act as miRNA sponges

MicroRNA sponging is a widely recognized functional mechanism of circRNAs, in which circRNAs competitively bind to microRNAs to modulate the expression of target genes. An illustrative example of this mechanism is observed in the case of circRNA_0026344, which functions as an anti-apoptosis factor in alveolar epithelial cells by sponging miR-21. This action inhibits miR-21's binding to PTEN. The overexpression of circ_0026344 has been found to partially block the CSE-induced autophagy and apoptosis, and certain blockages can be reversed by the introduction of a miR-21 mimic [70]. Whereas circBBS9, circ_0026466, and circ_0006872 have been identified as pro-apoptotic miRNA sponges against miR103a-3p/BCL2L13 (BCL2-like 13) axis, miR153-3p/TRAF6 (NF receptor associated factor 6) axis, and miR145/NF-κB axis, respectively [71–73]. It is worth noting that circRNA molecules have the potential to interact with multiple miRNAs. For example, circBBS9 has been found to also bind to miR-30e-5p to regulate the expression of ADAR, and exacerbate pulmonary inflammation in $PM_{2.5}$-induced COPD mice [74]. Similarly, recent studies have identified the involvement of circFOXO3 and circXPO1 in CS-induced inflammation in COPD. Specifically, circFOXO3 has been shown to enhance pulmonary inflammation by targeting miR-214 to upregulate IKK-β (inhibitor kappa B kinase β) expression, silencing of which would disrupt the NF-κB signaling pathway [75]; while circXPO1 has been found to interact with miR-23b-3p to upregulate TAB3 (MAP3K7 binding protein 3) in the TGF-β signaling pathway [76].

4.2. CircRNAs act as protein scaffolds

CircRNAs also possess the ability to interact with RNA bind proteins (RBPs) and serve as protein scaffolds to regulate gene expression [67]. A recent study showed that m^6A-modified circSAV1 forms a complex with YTHDF1 (YTH N6-methyladenosine RNA binding protein F1) and IREB2 (iron responsive element binding protein 2) mRNA, thereby facilitating the translation of IREB2. The upregulation of IREB2 disrupts iron homeostasis and ultimately leads to ferroptosis. In lung tissue of COPD patients, the level of circSAV1 level was found to be associated with the progression of COPD progression, whereas the silencing of circSAV1 in a mouse model effectively prevented CS-induced ferroptosis in lung epithelial cells [77]. Another circRNA, hsa_circ_0005045, was discovered to be upregulated in a specific subgroup of non-smoking $PM_{2.5}$-sensitive COPD patients. This circRNA was found to interact with PRDX2 (oxidized peroxiredoxin-2), a proinflammatory factor [78]. Interestingly, knocking down the corresponding circRNA, mmu_circ_0002950, in mice effectively rescued the $PM_{2.5}$-induced COPD-like lesions. These findings suggest that this circRNA plays a conserved role in protecting COPD patients against air pollution-associated acute disease exacerbation [79].

5. Therapeutic potentials of noncoding RNAs in COPD

Given the limited understanding of the underlying pathophysiological mechanisms of COPD, earlier therapeutics for COPD are largely adapted from the symptomatic treatments of asthma. The treatment options for COPD have significantly expanded in recent years, encompassing new oral and inhaled medications, as well as innovative surgical and bronchoscopic procedures. Nevertheless, the escalating global prevalence and mortality rates associated with COPD necessitate the development of safer and more effective pharmacological treatments for COPD.

Investigations into ncRNAs associated with COPD have not only identified novel therapeutic targets but have also offered alternative strategies for treating this disease [80]. RNA-based therapeutics, with their high specificity compared to small molecules and proteins and lower safety concerns compared to DNA therapies, have emerged as

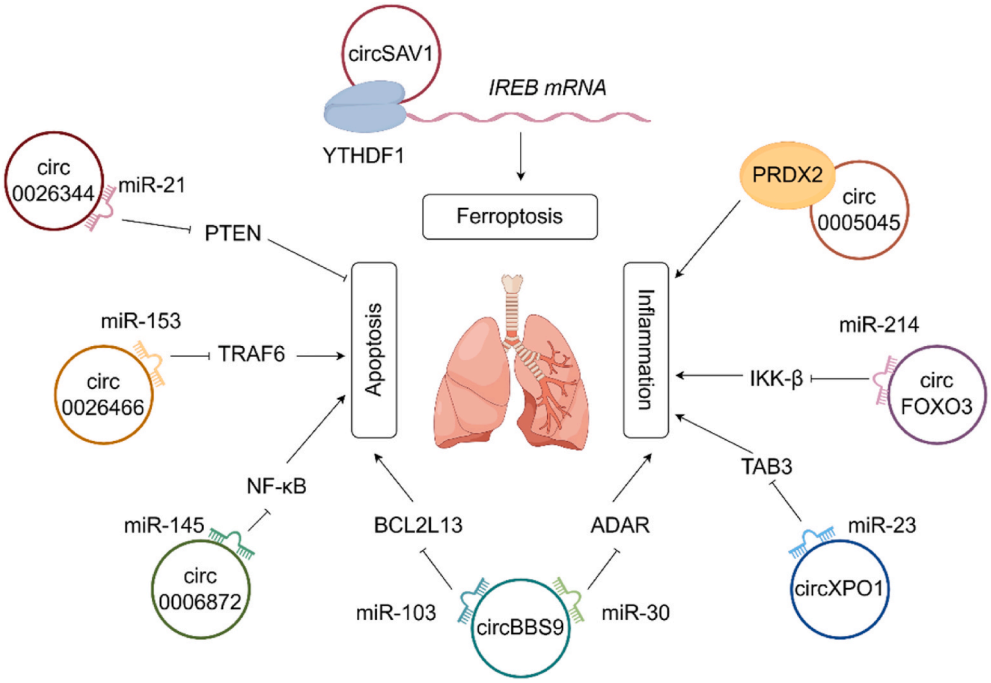

Fig. 2. Functional mechanisms of circRNAs in COPD development.

Table 3
Functional circRNAs validated in COPD models.

circRNA	Dysregulation in Patients	Target Gene/RNA	Targeted Pharmacological Actions	COPD models	Ref.
circ_0026344	Decreased in lung tissue	miR-21	Apoptosis	CS + BALB/c mouse	[70]
circBBS9	Increased in lung tissue	miR-30	Inflammation	$PM_{2.5}$+ICR mouse	[71,74]
		miR-103	Apoptosis	CSE + HPMEC	
circ_0026466	Increased in blood	miR-153	Apoptosis	CSE+16HBE	[72]
circ_0006827	Increased in lung tissue	miR-145	Apoptosis	CSE + HPMEC	[73]
				CSE + BEAS-2B	
circFOXO3	Increased in lung tissue	miR-214	Inflammation	CS + C57BL/6 mouse	[75]
				CSE + MLE12	
circXPO1	Increased in lung tissue	miR-23	Inflammation	CSE + MLE12	[76]
				CS + C57BL/6	
circSAV1	Increased in lung tissue	IREB2	Ferroptosis	CSE + BEAS-2B	[77]
				CS + BALB/c mouse	
circ_0005045	Increased in lung tissue	PRDX2	Inflammation	$PM_{2.5}$+C57BL/6 mouse	[78]

Abbreviations: CS, cigarette smoke; CSE, cigarette smoke extract; HPMEC, human pulmonary microvascular endothelial cell; PM, particulate matter.

promising therapeutic options for various diseases. The approval of Fomivirsen, the first RNA-based therapy, by the FDA in 1998 for the treatment of cytomegalovirus retinitis in immunocompromised patients highlights the potential of RNA drugs in clinical usage. Currently, over 10 RNA-based therapeutics have received FDA approval, and several comprehensive reviews have documented these achievements [81–83]. Furthermore, an array of RNA drugs, such as Vutrisiran (Phase 3 trial NCT04153149), Tivanisiran (Phase 3 trial NCT04819269), and Olparsiran (Phase 2 trial NCT04270760), are presently under clinical development. The expanded applications of these RNA-based drugs have demonstrated the feasibility of utilizing RNA-based therapeutics for the treatment of human diseases [84].

RNA-based therapies are also receiving growing attention in treating respiratory diseases with high specificity and potency [85]. In 2000, Stenton and colleagues conducted an initial investigation into the utilization of antisense oligodeoxynucleotide (ASO) in the treatment of respiratory diseases. Specifically, ASO targeting spleen tyrosine kinase (Syk) was administered via aerosol to the lungs of mice to assess its efficacy in managing asthma [86]. However, due to issues of non-specificity and potential allergic reactions, further exploration of Syk ASO was halted. The challenge of achieving targeted delivery of RNA molecules to specific cells emerged as a significant barrier to the implementation of RNA therapies for pulmonary conditions. Attempts have been undertaken over the past two decades to enhance the pulmonary delivery of therapeutic RNAs. In 2008, Xu et al. developed a poly(ester amine)-mediated complex that effectively delivered AKT siRNAs via aerosol, leading to the inhibition of lung cancer progression [87]. Subsequently, in 2014, nanoparticles were utilized for the delivery of miR-34 to lung cancer cells, resulting in the successful inhibition of tumor growth in vitro [88]. And TargomiR, utilizing both a nanoparticle drug delivery system and an anti-epidermal growth factor receptor antibody to target miR-16 mimics to cancer cells, has completed phase I clinical trials for the treatment of malignant pleural mesothelioma and non-small cell lung cancer (NCT02369198) [89]. Noticeably, in addition to its efficacy in treating respiratory diseases, recent advancements in nanotechnology-based miRNA therapies have also demonstrated potential for early diagnosis and overcoming drug resistance in lung cancer treatment [90].

Efforts have also been undertaken to address critical pathways involved in the pathogenesis of COPD using RNA interference (RNAi) approaches (Table 4). This approach has been favored due to the ease of synthesizing small interfering RNAs (siRNAs) and their successful application in various other diseases [91]. Specifically, to mitigate inflammation in the airway epithelium and alveolar macrophages of COPD patients, siRNAs specific to the receptor-interacting serine/threonine-protein kinase 2 (RIP2) and ribosome protein S3 (RPS3) have been designed. Both of them are crucial factors involved in the NF-κB signaling pathway, a master proinflammatory regulator in COPD progression [92,93]. To mitigate airway remodeling and associated lung fibrosis, CHST3 (carbohydrate sulfotransferase 3) -specific siRNA and TROP2 (trophoblast cell surface antigen 2) -specific siRNA were employed to reduce emphysema and basal cell hyperplasia [94,95]. Additionally, to counteract pulmonary vascular remodeling, which may further lead to pulmonary arterial hypertension, siRNAs targeting HIF-1α and HIF-2α were utilized to inhibit smooth muscle cell proliferation and EMT [96].

Table 4
Current studies for RNA-based therapeutics in COPD.

Therapeutic target	RNA type	Delivery system	Target cell	Ref.
RPS3	siRNA	Naked siRNA	Macrophage	[92]
RIP2	siRNA	Lipofectamine	Macrophage Epithelial cell	[93]
CHST3	siRNA	Naked siRNA	Macrophage	[94]
TROP2	siRNA	Lipofectamine	Basal cell	[95]
HIF1/2	siRNA	Lipofectamine	Pulmonary artery smooth muscle cells	[96]

Presently, many siRNAs have demonstrated promising outcomes in mitigating inflammation, airway and vascular remodeling, and disease exacerbation in COPD models [70]. However, breakthroughs in the development of RNA-based drugs for COPD treatment have not emerged yet. Similar to other respiratory conditions, the primary obstacle in utilizing RNA therapies for COPD lies in achieving effective and specific delivery. Pulmonary delivery of inhaled RNA drugs is preferred and rapidly advancing due to its minimal patient discomfort [97]. Inhaled drugs may encounter interference from endogenous lung substances and various lung cell types prior to reaching their intended therapeutic targets. A thorough comprehension of the pathological microenvironment is imperative for the successful design and precise targeting of inhaled RNA drugs. Presently, the insufficient understanding of the diverse pathophysiological mechanisms contributing to the initiation and advancement of COPD appears to impede the advancement of RNA-based therapies for COPD treatments. Extensive endeavors are still required to elucidate the intricate networks involved in COPD pathogenesis and to identify pivotal regulatory factors for therapeutics. Meanwhile, the mitigation of undesirable off-target effects poses another significant obstacle, particularly for those genes and ncRNAs that exhibit multifunctionality across various pathways.

In summary, a multitude of ncRNAs have been unearthed as pivotal contributors to the prevalence of COPD. The functional investigations conducted on ncRNAs have substantially augmented our comprehension of the intricated network underpinning COPD pathogenesis, thereby presenting a novel avenue for the identification of therapeutic targets and drugs for COPD management.

CRediT authorship contribution statement

Bingbing Ren: Writing – original draft, Funding acquisition. **Hua Su:** Writing – review & editing, Funding acquisition. **Chang Bao:** Writing – review & editing. **Hangdi Xu:** Writing – review & editing. **Ying Xiao:** Writing – review & editing, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

This work was supported by the National Science Foundation of China (32000437), the Medical Science and Technology Project of Zhejiang Province (2023RC188, 2022RC037, 2024KY105), and the Opening Project of Zhejiang Provincial Preponderant and Characteristic Subject of Key University (Chinese Traditional Medicine), Zhejiang Chinese Medical University (ZYXZD2019003). Figures were created by FigDraw (FigDraw.com).

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