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Extracellular microRNAs, long non-coding RNAs and circularRNAs in chronic obstructive pulmonary disease

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Highlights:

- The pathway of a healthy to an inflammatory lung, resulting in COPD.
- COPD is a chronic inflammation in the lung characterized by immune activity involving mast cells, basophils, lymphocytes subsets and cytokines.
- NcRNAs, including miRNAs, lncRNAs and circRNAs are involved in COPD, regulating the translation of their target mRNAs by inhibition or interaction among each other.
- Ras signaling pathway, MAPK signaling pathway, and oxidative stress are involved in the pathogenesis of COPD.
- Advancements in the development of therapies using immune molecules or ncRNA as targets may improve the course of disease of COPD.

Abstract: Chronic obstructive pulmonary disease (COPD) is a progressive inflammatory disease of the respiratory system characterized by persistent difficulties of breathing and dyspnea. COPD patients display emphysema, the anatomic destruction of lung parenchyma accompanied with a high risk for cardiovascular disease, lung cancer, and mortality. The disease is not treatable. Therefore, identifying blood-based biomarkers of COPD, such as non-coding RNAs (ncRNAs), may facilitate early diagnosis, understanding of the molecular basis of COPD and advancement of development of targeted therapies. There is accumulating evidence that dysregulation of ncRNAs plays a crucial role in a variety of diseases, including COPD. The current review gives an overview on extracellular ncRNAs, with a particular focus on microRNAs (miRNAs), long non-coding RNAs (lncRNAs) and circularRNAs (circRNAs) in plasma and serum of COPD patients. In addition, the potential role of exosomes carrying ncRNAs from cells to cell in the pathogenesis of COPD is also discussed. Furthermore, the characteristics of these ncRNAs along with their interplay among each other are additionally considered.

Keywords: COPD; GOLD stage; exacerbation; inflammation; miRNA; lncRNAs; circRNAs; targeted therapies; biomarkers

1. Introduction

Chronic obstructive pulmonary disease (COPD) denotes a heterogeneous assembly of lung diseases, and includes chronic bronchitis and bronchiectasis with peribronchiolar fibrosis, as well as overinflated alveoli along with alveolar wall destruction, such as pulmonary emphysema. This inflammatory disease destroys the cilia on the inner surface of the bronchi. Normally, the cilia are mobile and covered by a thin layer of mucus. There is a self-cleaning process in which pathogens from the air are usually trapped by this mucus film and do not enter the lungs. The cilia then transport the mucus out of the bronchi. However, if the cilia are destroyed, the mucus can no longer be properly removed, and the bronchi become blocked. COPD is an incurable, permanently damaged lung disease with a narrowed respiratory tract. The main catalyst is smoking hence it is essential to stop smoking. Further causes of the development of COPD are permanently inflamed bronchi. A chronic bronchitis can develop if the respiratory tract is frequently exposed to pollutants, such as tobacco smoke or environmental factors. COPD develops slowly over the years. Initial symptoms, such as a persistent cough, are often mistaken as another disease, such as smoker's cough, bronchitis, or asthma. Typical symptoms of COPD include cough with sputum production, wheeze, dyspnea during daily activities, such as climbing stairs and talking during a walk [1]. During exacerbations, COPD patients are at risk for severe cardiovascular disease [2]. The majority of COPD patients are over 60 years old. Their treatment aims to stop or at least slow down its progression [3]. Diagnosis of COPD requires lung function tests, such as spirometry [4].

Experts classify COPD into four different Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages. For the classification, the FEV1 (forced expiratory volume 1) value is essential, indicating a one-second forced exhalation, namely the amount of air which a patient can exhale as quickly and forcefully as possible within one second. In this respect, the FEV1 value is > 80%, > 50%, > 30% and < 30% for mild GOLD 1, moderate GOLD 2, severe GOLD 3 and very severe GOLD 4 stages, respectively [5,6].

Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses recommended that signals, namely Ras signaling pathway, MAPK signaling pathway, and oxidative stress may be involved in the pathogenesis of COPD.

The principal pathophysiology of COPD encompasses an intricate interplay of various inflammatory factors, including processes, such as T cell-mediated secondary inflammatory responses, activation of macrophages and neutrophils, as well as impaired epithelial barrier function. The inflammatory response causes frequent exacerbations and disease progression. Therapies that suppress the inflammatory response may expand pulmonary function, and improve prognosis and life quality of COPD patients [7].

COPD patients are treated with medications that dilate the airways, namely bronchodilators that aim to reduce swelling of the mucous membranes. Inhaled cortisone is also used reducing the risk of inflamed airways. Furthermore, ipratropium is a commonly medication for COPD patients, as well as ingredients including beta-2 agonists, which contain substances such as terbutaline, salbutamol, or fenoterol [8]. The current treatment strategies are focused to minimize symptoms and reduce the risk of a future attack, but they have only few anti-inflammatory activities in avoiding or reducing disease progression. Therefore, the discovery of new prognostic and diagnostic markers is crucial to enhance the care and therapy of COPD patients. Such factors could be non-coding RNAs (ncRNAs) that encompass microRNAs (miRNAs), long-non coding RNAs (lncRNAs) and circular RNAs (circRNAs). Their central function is their ability

to downregulate the expression of protein-encoding mRNAs [9]. In addition, competitive endogenous RNAs (ceRNAs) may act as sponges for miRNAs through interacting with their binding sites, modulating the miRNA activity [10–12]. Apoptotic and necrotic cells discharge them into the blood circulation, where they circulate both cell-freely or associated with Argonaut proteins [13]. Within the bloodstream, ncRNAs can also be detected in exosomes which are actively secreted by various cells. Exosomes are able to carry ncRNAs from cell to cell, to change the features of the recipient cells that uptake these exosomes [14].

The current review article gives an overview on miRNAs, lncRNAs and circRNAs that circulate cell-freely or in exosomes in plasma and serum of COPD patients. It focuses, therefore, on ncRNAs in COPD, because their dysregulated levels contribute to modulate different signaling pathways and consequently, regulate the translation of a variety of mRNAs, resulting in a change of cellular behavior. This altered expression of ncRNAs in different diseases, including COPD, make them to excellent targets to design specific therapeutic interventions. The review deals with the inhibitory function on the mRNA translation of inflammatory factors by these ncRNAs, with a special focus on the immune system. The potential role of ncRNAs in prognosis, diagnosis and treatment of COPD patients is also discussed.

2. Immune system in COPD

COPD patients display a chronic inflammation in the lung characterized by immune activity involving mast cells, basophils, lymphocytes subsets and cytokines (Figure 1).

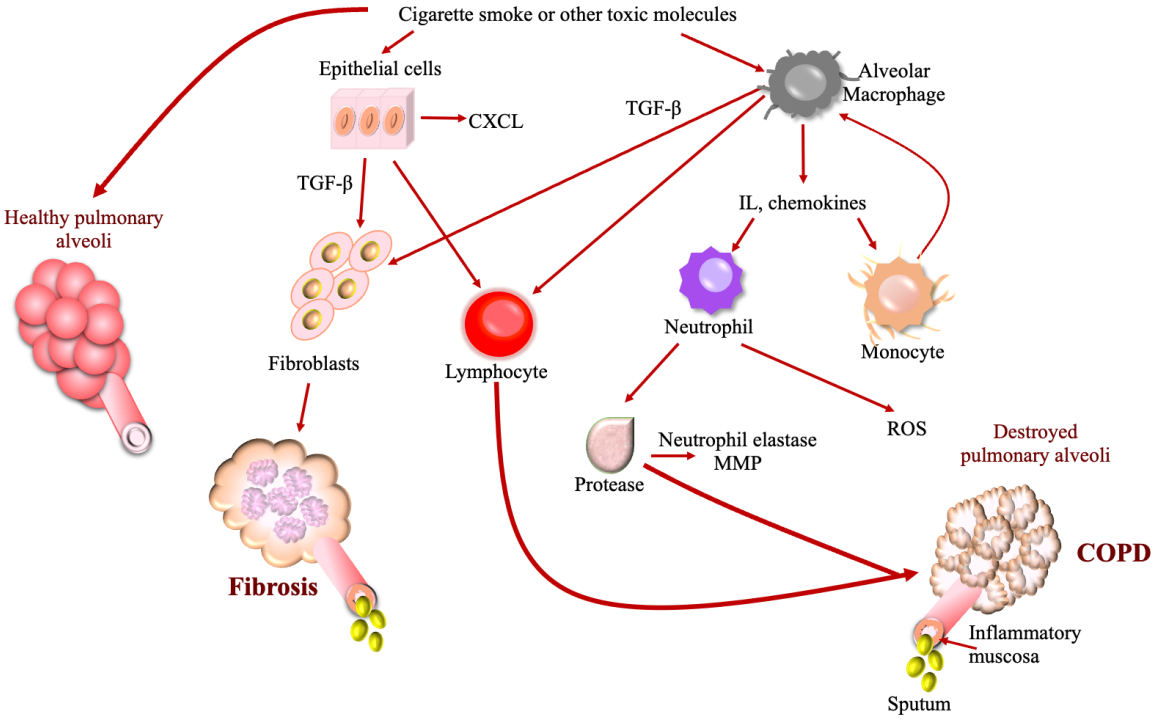

Figure 1. The pathway of a healthy to an inflammatory lung. Cigarette smoke or other toxic molecules activate epithelial cells that in turn stimulate fibroblasts and lymphocytes that are involved in the inflammatory process in the lung. The release of cytokines and chemokines by alveolar macrophages activates neutrophils to generate proteases that participate in the destruction of the lung. This inflammatory is described in more detail in the text below.

The immunopathology of COPD is exerted by innate and adaptive inflammatory immune responses due to the long-lasting smoking of cigarette and environmental factors [15]. A large, complex cross-talk between lymphocytes, monocyte-derived dendritic cells and macrophages triggers both cell-mediated and antibody-mediated chronic inflammation [8]. It was reported that the gravity of COPD rises the number of CD4+ helper and CD8+ cytotoxic T lymphocytes in the small airways [16]. Specific antigen presenting cells (APCs), including T cells and dendritic cells initiate the immune response. APCs play an important role in the recognition, processing and presentation antigens to T cells mediated by MHC molecules [17]. For an efficient immune response, an antigen-specific interaction between B and T cells are crucial and necessitate MHC class II complexes on the B cell to associate with the T cell receptor on antigen-specific T cells [18]. Natural killer (NK) cells present innate lymphoid cells and crosstalk with T and B cells. They generate high levels of cytokines, e.g., interferon-γ (IFN-γ), IL-10, IL-13, tumor necrosis factor (TNF)-α and granulocyte-macrophage colony stimulating factor (GM-CSF). They induce cell cytotoxicity by stimulating the cell killing proteins granzyme and perforin [19]. Macrophages are myeloid immune cells. When activated, they protect against bacterial pathogens by intensifying a pro-inflammatory response that is characterized by the discharge of inflammatory cytokines, e.g., IL-1β, IL-12, IL-6 and TNF-α, aside from nitrogen species and reactive oxygen. Activated macrophages comprise M1 and M2 macrophages that predominantly participate in pro-inflammatory responses and anti-inflammatory responses, respectively [20].

2.1. Lymphocytes

COPD patients have increased concentrations of activated macrophages and neutrophils in their sputum. In addition, there are increased levels of lymphocytes in the lungs, such as $CD8^+$ T cells which prevail over $CD4^+$ T cells [21]. In the lung, cytotoxic T cells express a higher number of bacterial Toll-like receptors (TLR), suggesting their regulation by colonizing bacteria [22]. Recruitment of cytotoxic T cells and T helper cells together with activated lymphoid cells may contribute to exert neutrophilic inflammation in COPD. There is also a high number of innate lymphoid cells that together perpetuate the neutrophilic inflammation in the lung of COPD patients. The association between CXC-motive-chemokine receptor 3 (CXCR3), which is produced by CD8+ T cells and its ligand CXCL10 significantly increases the synthesis of matrix metalloproteinase-12 (MMP12) by macrophages, and is essential for the initiation of emphysema. Besides, activated macrophages exert their pathogenic effect on disease progression by releasing the protease neutrophil elastase which breaks down elastin and thus, contributes to the development of pulmonary emphysema. The increased levels of neutrophil elastase in the lung of COPD patients cause mucus hypersecretion. Furthermore, activated macrophages release IL8 which is an effective chemoattractant for the recruitment of neutrophils in the airway. The transfer of neutrophils from the bloodstream into the airways provokes a rise of neutrophils in lung excretions [23]. In this respect, high amounts of neutrophils are considered as initiators of the inflammatory processes and mobilized by IL8 and CXCL2, as observed in blood, bronchoalveolar lavage fluid, sputum and lung biopsies of COPD patients. Epithelial cells and macrophages also export transforming growth factor β (TGF-β), which activates fibroblast proliferation, promoting fibrosis in small airways. The increased number of mast cells, tissue-resident granulocytes in the alveolar tissue of COPD patients refers to the disease severity [24,25] (Figure 1).

2.2. Cytokines

Numerous proinflammatory cytokines, e.g., interleukins IL-1, IL-6, IL-8, IL-10, IL-18 and IL-32, and TNF-α and IFN-γ, produced by immune cells in response to infection or injury, initiate a cascade of events that trigger the inflammatory process of the pathogenesis of COPD [26]. For example, activated epithelial cells are involved in the release of TGF-β**,** TNF, IL-1β, IL-6 and IL-8. IL-8 is known to play an essential role in the inflammatory reaction of COPD, activating neutrophils to the inflammatory region of the lung [27]. Recruitment of macrophages leads to a release of IL-1α, IL-1β, IL-33 and IL-18. Inflammation of eosinophilic granulocytes is involved in a release of IL-5 and IL-13 in response to prostaglandin D2 [8]. Furthermore, high levels of IL-17 were detected in sputum of COPD patients [28].

2.3. Chemokines

The homeostatic CXC motif chemokines include the CXC ligands CXCL 12, CXCL 13, CXCL 21, and CXCL25, whereas the proinflammatory chemokines include CXCL1, CXCL2, and CXCL8. This category of cytokines plays a crucial role in the inflammatory process in COPD, regulating leukocyte migration. CXCL9, CXCL10, and CXCL11 bind to CXCR3 with different affinity. T cells that express this common receptor CXCR3 were observed in a larger proportion of COPD patients with markedly impaired lung function [29]. Cigarette smoke causes an inflammatory cascade that activates the recruitment of macrophages into the respiratory tract, that release an increased number of chemokines and are main producers of chemokine ligands. During exacerbation, there is a correlation of the levels of chemokine ligands with those of the neutrophil number in sputum, as well a correlation of CXCL8 levels with those of the neutrophil-associated proinflammatory enzyme, myeloperoxidase in the blood [30]. Slowly, there are some advancements in the therapy of COPD patients. So, a phase IIb clinical trial showed that a CXCR2 inhibitor was able to reduce pulmonary inflammation and postpone the inception of the first exacerbation [31].

3. COPD-associated mediators

3.1. Oxidative injury

Oxidative stress also contributes to COPD, in particular to age-related COPD [32]. It may lead to an impaired innate macrophage activation, namely reprogramming of alveolar macrophages with a shift from M1 towards partial M2 polarization, correlating with COPD severity [33]. In the oxidative process, NADPH oxidase (NOX) plays an essential role. It metabolizes molecular O_2 to generate reactive oxygen species (ROS) that in turn cause mitochondrial dysfunction and impaired adaptive antioxidant responses. Intracellular ROS can cause the peroxidation of membrane lipids, DNA strand breaks, enzymatic activity alterations, and affect signaling pathways. ROS target epithelial cells in the alveoli, local macrophages, and pulmonary fibroblasts that are a secondary source of ROS. However, investigations have failed to provoke significant effects of anti-oxidant supplementation in order to prevent chronic disease, and even suggest an enhancement of mortality by these anti-oxidant agents [34]. Nevertheless, alterations in the expression of NOX which is involved in redox homeostasis may be an auspicious strategy for the treatment of COPD patients.

3.2. Unbalanced proteolysis and alpha-1-antitrypsin

Unbalanced proteolysis leads to proteolytic degradation of the extracellular matrix (ECM) and generates fragments that may act as chemokines, promoting inflammation. Explicitly, laminin and fibronectin fragments are chemotactic to neutrophils and monocytes [35].

In COPD, neutrophils and macrophages may produce large amounts of proteases that destroy the tissue, leading to decreased levels of elastin. Inflammatory cells may create a proteolytic environment which mainly contains neutrophil-derived protease and elastase, macrophage-derived matrix metalloproteases. For example, the anti-proteolytic protection is mediated by the so-called protease inhibitor alpha-1-antitrypsin (AAT). It is a glycoprotein, mainly generated in the liver and protects against proteases to avoid the degradation of tissues. It inhibits the function of enzymes, especially trypsin and neutrophil elastase. In the lung, leukocytes release neutrophil elastase to eliminate foreign molecules. The quantity and lifespan of these beneficial enzymes are regulated by ATT. Consequently, dilation or destruction of the lung lobules is often associated with a deficit in ATT [36,37]. ATT deficiency is triggered by mutations in SERPINA1 which encodes ATT, leading to the accumulation of misfolded ATT and low levels of ATT in the blood circulation. Treatment of ATT-associated lung emphysema includes augmentation therapy, namely periodic intravenous infusions of pooled human plasma-derived, purified AAT. New therapies that deal with the targeting of misfolded ATT are currently under development [38,39].

3.3. Epigenetic changes

Examples of epigenetic modulations are DNA methylation, post-translational modifications of histones and the expression of ncRNAs. Numerous genes associated with epigenetic changes have been reported in COPD. For example, signal cascades of G-protein-coupled receptor, tensin homolog (PTEN), aryl hydrocarbon receptor, cAMP-mediated, phosphatase and nuclear factor erythroid-derived 2-related factor 2 (Nrf2), and oxidative stress response are subject to epigenetic changes [40].

4. Dysregulated signaling pathways in COPD

Among the signaling pathways that contribute to COPD, the nuclear factor kappa-B (NF-κB), phosphoinositide 3-kinase (PI3K), mitogen-activated protein kinase (MAPK), and Wnt/β-catenin signaling pathways are to mention [41]. These dysregulated signaling pathways support inflammation, oxidative stress, and endothelial dysfunction, which are critical drivers of COPD.

4.1. NF-κB pathway

The NF-κB pathway starts with the activation of the IκB kinase (IKK) triggered by the stimulation of various extracellular signals including TNF-α and IL-1β. In turn, IKK phosphorylates the IκBα protein, resulting in ubiquination and dissociation of IκBα from NF-κB, and eventual degradation of IκBα by proteasomes. Then, stimulated NF-κB is translocated from the cytoplasm into the nucleus to activate the transcription of target genes, resulting in the regulation of proinflammatory cytokine production and leukocyte recruitment [42]. In addition, the NF-κB pathway induces oxidative stress, leading to exacerbate lung injury in COPD patients. Oxidative stress enhances the expression of redox-sensitive

transcription factors, namely NF-κB and activator protein 1 (AP-1), leading to the release of e.g., IL-1β and TNF-α [43]. The elicited accumulation of reactive oxygen species (ROS) which is involved in DNA methylation, reduces the activity of histone deacetylases (HADC) and consequently, augments the activity of histone acetyltransferase which causes in turn the accumulation of inflammatory cells, in particular neutrophils [44].

4.2. PI3K/Akt pathway

The stimulation of the PI3K/Akt signaling pathway mainly occurs by tyrosine kinase and G protein-coupled receptors. Following receiving the signal, the p110 and p85 regulatory subunits of PI3K convert phosphatidylinositol 2 phosphate (PIP2) to phosphatidylinositol 3 phosphate (PIP3). In turn, PIP3 associates with protein kinase B (Akt), and moves to the cell membrane for activation [45]. In COPD patients, the nuclear factor erythroid 2-related factor Nrf2 is a PI3K/Akt downstream signaling target, and its expression correlates with oxidative stress response, resulting in the release of inflammatory factors. On the other hand, the persistent lung inflammation initiaties neutrophil accumulation by stimulating the PI3K/Akt pathway. The assembly of associated cells produces high levels of ROS to promote additional exacerbation of oxidative stress. The stimulation of the PI3K/Akt pathway also decreases HADC activity, resulting in glucocorticoid insensitivity [46].

4.3. MAPK pathway

The PI3K/AKT/mTOR and MAPK/RAS/RAF/MEK/ERK pathways cooperate with each other at various positions. The activation of the MAPK cascade occurs by growth factors and cytokines that bind to G-protein-coupled receptors, receptor tyrosine kinases, and non-nuclear activated steroid hormone receptors. The elicited signals stimulate a series of protein kinase cascades, including MAPKs and MEKs [47] which in turn, stimulate cytokines, neurotransmitters and serine proteases leading to oxidative stress and inflammatory responses. In COPD, IL-8 and TNF-α are regulated by p38MAPK. The excessive secretion of these inflammatory factors eventually causes the assembly of neutrophils and serine proteases, destructing the lung structures. In addition, IL-8 and TNF-α seem to mediate glucocorticoid insensitivity in COPD patients, impairing the function of glucocorticoid receptor by phosphorylation, whereas anti-inflammatory effects of glucocorticoids are exerted by this receptor [48].

4.4. Wnt/β-catenin pathway

The Wnt/β-catenin signaling pathway is initiated by binding of WNT ligands to the transmembrane receptor Frizzled (FZD) protein, whereat the low-density lipoprotein receptor-related protein (LRP) 5/6 membrane proteins perform as co-receptors. The signal de-represses the transcriptional co-activator β-catenin that monitors key programs of developmental gene expression [49]. Reduced WNT-β-catenin signaling is associated with impaired lung repair in COPD and contributes to COPD pathogenesis [50].

5. Characteristics of ncRNAs

NcRNAs, including miRNAs, lncRNAs and circRNAs are involved in benign and malignant diseases, regulating mainly the translation of their target mRNAs by inhibition [51,52]. NcRNA can also interact

with each other to impede the inhibitory effect on mRNA translation by the sequestered ncRNA (Figure 2). This ceRNA activity of ncRNAs makes the regulatory network across the transcriptome more complex, and it is challenging to predict which interactions between ncRNAs is happening as well as their impact on the signaling pathway network and the cellular conduct. The interaction is dependent on the concentration, character and subcellular distribution of the ncRNAs and defines the ceRNA activity. Thus, the ceRNA activity plays a crucial role in regulatory network and creates a modified cellular protein expression profile that should also be elaborated in pathological conditions [53] (Figure 2). NcRNAs are released from the cells either passively as cell-free molecules or actively by exosomes into the blood circulation [54,55]. Exosomes can transfer ncRNAs from cell to cell and propagate the function of ncRNAs in a variety of cells. The uptake of these exosomal ncRNAs in a recipient cell modulates the characteristics of this cell. Hence, exosomal ncRNAs play an essential role in cell-to-cell communication, to e.g., spread inflammation in the lung [14,56,57].

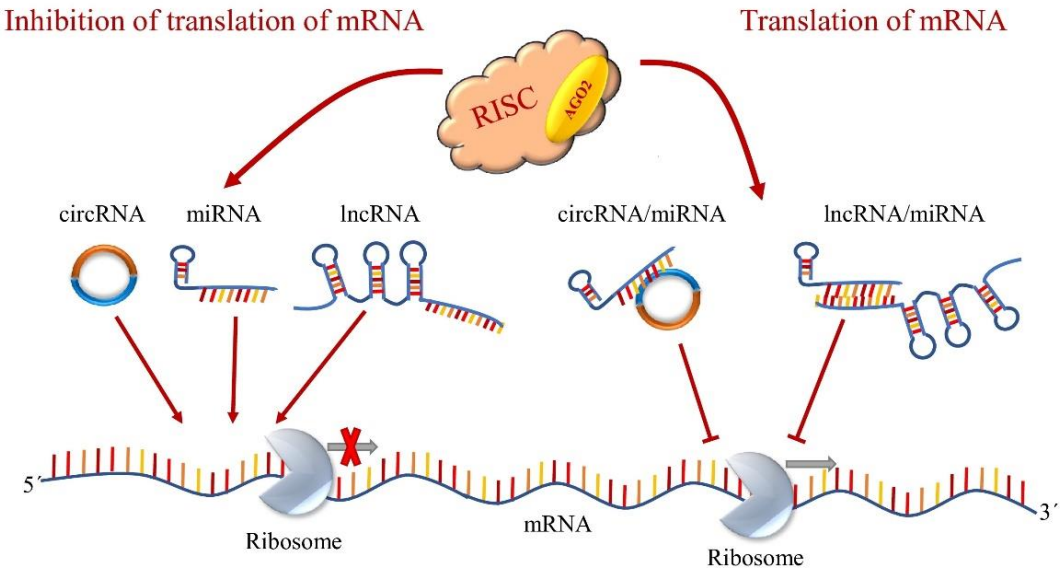

Figure 2. Interplay of miRNAs, lncRNA and circRNA in the regulation of mRNA expression. In the RISC (RNA-induced silencing complex) occurs the regulation of mRNA by ncRNAs. NcRNAs bind to their mRNA target sequence and inhibit the translation of mRNA. The interaction of circRNA and lncRNA with miRNA abrogates the inhibition of translation of mRNA, and the ribosomes can translate mRNA into protein. The arrows directly above the mRNA show the direction of the ribosomes to translate the mRNA.

5.1. miRNAs

MiRNAs are short ncRNA molecules of about 22 nucleotides at size. They are involved in both mRNA silencing and post-transcriptional regulation of gene expression [58]. They mediate their effects by stimulating mRNA decay and translation arrest of protein-encoding mRNAs as well as genes encoding for lncRNAs. This occurs in the argonaute-containing protein complex termed RISC (RNA-induced silencing complex) which integrates the mRNA and ncRNAs. The complementary miRNA base-pairing

either cleaves the mRNA strand into two fragments, or destabilizes the mRNA through truncating its poly(A) tail. This process leads to the inhibition of translation of the mRNA into proteins by ribosomes [59].

Biogenesis of the miRNA starts in the nucleus, where the long primary miRNA (pri-miRNA) transcribed by RNA polymerase II is cut by the endonuclease Drosha to generate the 60–70-nucleotide stem-loop precursor miRNAs (pre-miRNAs). The pre-miRNA is transferred from the nucleus to the cytoplasm by exportin 5, and is in turn processed by DICER1 with the help of the RNA-binding protein transactivation-responsive RNA-binding protein (TRBP) to generate the mature duplex miRNA. One or both of the mature miRNA strands is loaded into RISC containing AGO proteins and DICER1 to exert their function [60]. An alternative pathway of the miRNA maturation was also described. Here, mirtrons bypass the Drosha processing step, whereby the pre-miRNA is generated by a splicing reaction [61]. Besides, miRNAs can also be cleaved and generated from lncRNAs [62,63].

5.2. lncRNAs

LncRNAs are transcripts displaying a length over 200 nucleotides. They have a broad scope of action, regulating gene expression at post-transcriptional and epigenetic, transcriptional levels. Similar to miRNAs, lncRNAs inhibit the translation of their target mRNAs [64]. LncRNAs have ceRNA activity, sponging miRNAs to hinder miRNAs to carry out their inhibitory effect on target mRNAs [11,65]. In this regard, high-throughput sequencing was conducted by Shan *et al.* [66] to detect modulations in the expression of lncRNAs and mRNAs in plasma exosomes. They detected 1578 differentially regulated lncRNAs and 3071 differentially regulated mRNAs that may participate at the pathogenesis of COPD. They established a lncRNA-miRNA-mRNA network to predict the potential communications among these RNAs [62].

The biogenesis of lncRNAs corresponds to mRNA transcription by RNA polymerase II. Due to their location relative to protein-coding genes, they are arranged into antisense, enhancer, bidirectional, intronic transcript lncRNAs, and large intergenic ncRNAs. Furthermore, lncRNAs can display different isoforms from the same locus, evolving either with or without polyadenylation, alternative cleavage, and splicing [67].

5.3. circRNAs

CircRNAs are covalently closed loop structures and have, therefore, no 3′ and 5′ ends. This stable ring structure inhibits their degradation by exonucleases, resulting in longer half-life of circRNAs of over 48 hours compared of linear RNAs with 10 hours [68]. Due to biogenesis, circRNAs are organized in three subtypes, exonic circRNAs (ecRNAs), exon-intron circRNAs (EIciRNAs), and circular intronic RNAs (ciRNAs) [69]. They either activate gene transcription by attaching to DNA polymerase II or prevent mRNA translation. However, the majority of circRNAs have ceRNA activity, regulating gene expression by sponging miRNAs [70,71]. Four classical models describe the biogenesis of circRNAs: (1) In the lariat-driven circularization model, the pre-mRNA is folded by nonadjacent exons in close proximity to each other, stimulating exon-skipping and back-splicing. (2) In the intron-pairing-driven circularization model, the base pairing of long flanking complementary introns, including Alu elements, initiates back-splicing. (3) In the RNA-binding protein (RBP)-driven circularization model, RBPs associate with introns that flank at both ends of an exon and join them for back-splicing. (4) In the ciRNA biogenesis, debranching enzymes degrade intron lariats. However, GU- and C-rich elements in the 5′ and 3′-end allow the escape of introns for this debranching [72].

6. Deregulated ncRNAs in COPD

The following paragraphs give an overview on the studies that so far, have dealt with extracellular miRNAs, lncRNAs and circRNAs in the blood of COPD patients. The described deregulation of ncRNAs in COPD patients may not be disease-specific. Implying that they may also be deregulated in other diseases. They can also either up- or downregulated in patients with different diseases [52].

As shown in the following tables, the studies have investigated miRNAs, lncRNAs and circRNAs in plasma, serum or exosomes of patients with different COPD stages, as well as analyzed variable ncRNA targets in different signaling pathways [40]. However, ncRNAs can bind to several target in several signaling pathways. They can also act deal as ceRNAs. In addition, the studies applied different techniques (e.g. qPCR, RNA microarray or RNA sequencing) to determine the levels of extracelluar ncRNAs in relatively small, heterogenous patient cohorts. This flood of unrelated data on miRNAs, lncRNAs and circRNAs makes it difficult to interpret the essential connotation of these studies, and whether these ncRNAs have the potential to enter the clinic. Therefore, investigations should concentrate on the use COPD patient cohort with similar parameters, same techniques and same tissue samples. Thus, multicenter studies with consistent analyses plans would be helpful.

6.1. Analyzed extracellular miRNAs in COPD

Numerous miRNAs have been reported to play a crucial role in COPD [73]. Table 1 gives a summary of studies on deregulated extracellular miRNAs and their targets detected in COPD. Table 1 does not demand to show all publications on the research of extracellular miRNA in COPD but it shows an informative overview on the wide-ranging action of miRNAs in a variety of pathways.

Table 1. Deregulated extracellular miRNAs detected in COPD.

miRNAs	Correlations*	Source	Ref.
miR-19b, miR-125b, miR-320c		Plasma	[74]
miR26, miR-3529	CDC42/MAPK	Plasma, bronchoalveolar lavage	[75]
miR-29b	BRD4, IL-8	Plasma	[76]
miR-103, miR-142, miR-30b, miR-342	Heart failure	Plasma	[77]
miR-106, miR-486	SP-D	Plasma	[78]
miR-106b		Plasma	[79]
miR-125b	TNF-α, IL-1β, IL-8, LTB-4	Plasma	[80]
miR-126	TNF-α, IL-1β, IL-6, IL-17	Plasma	[81]
miR-145, miR-338, miR-3620		Plasma	[82]
miR-150	IRE1*α*, IL-6, IL-8, COX-2	Plasma	[83,84]
miR-150	leukocytes, C-reactive protein	Plasma	[84]
miR-196, miR-361	ARHGEF12, abca1, mTOR	Plasma	[85]
miR-210		Plasma	[86]
miR-218		Plasma	[87,88]
miR-422	SMAD4, TGF-β, muscle mass	Plasma	[89]
miR-423	duration of smoking	Plasma	[90]
miR-499	NF-kB	Plasma	[91]
miR-543	IL-33	Plasma	[92]
miR-191	NF-kB/IL-8	Plasma exosomes	[56]

Table 1. *Cont.*

miRNAs	Correlations*	Source	Ref.
miR-92b-3p, miR-374a, miR-106b-3p	Cytokine-cytokine receptor	Plasma exosomes	[57]
miR-1	MRTF-SRF	Serum	[93]
miR-7, miR-20a, miR-28, miR-34c, miR-100		Serum	[94]
miR-15b, miR-23a, miR-26b, miR-148a, miR-223		Serum	[95]
miR-21, miR-181a		Serum	[96]
miR-22	HDAC4-DLCO	Serum	[97]
miR-92a, miR-221	TNF-α, IL-8, IL-1β, TGF-β1	Serum	[98]
miR-132	SOCS5	Serum	[99]
miR-134, miR-1233	Acute pulmonary embolism	Serum	[100]
miR-145	PI3K/Akt/mTOR	Serum	[101]
miR-146a, miR-146b	TNF-α, IL-1β, IL-6, IL-8, LTE-4, IL-1β and LTB-4	Serum	[102]
miR-206	HIF-1α/Fhl-1	Serum	[103]
miR-218	IL-6, IL-8, TNFR1, p–p65	Serum	[104]
miR-301a	MBD2/ /CXCL12/CXCR4	Serum	[105]
miR-1246		Serum	[106]
let-7	IL-6, myofibroblast differentiation	Serum	[107]
miR-1258	Neutrophile	Serum exosomes	[108]

*BRD4, bromodomain 4; CXC, C-X-C motif chemokine; COX-2, cyclooxygenase-2; DLCO, Capacity of the lungs for carbon monoxide; EZH2, enhancer of zeste homolog 2; Fhl-1, Four and A half LIM domains 1; HDAC4, Histone deacetylase 4; HIF-1α, Hypoxia inducible factor 1 subunit alpha; IGFBP3, Insulin-like growth factor binding protein 3; IL, interleukin; IRE1α, inositol requiring enzyme 1α; LTB4/E4, leukotriene B4/E4; MBD2, Methyl-CpG-binding domain protein 2; PPA2, pyrophosphatase 2; SOCS5, Suppressor of cytokine signaling 5; SP-D, surfactant protein D; TGF-β, tumor growth factor-β; TNF-α, tumor necrosis factor-α; TNFR1, tumor necrosis factor receptor 1.

In the following, some examples from the Table 1 are described in more detail:

As shown by Bersimbaev *et al.* [74], the expression levels of miR-19b were increased in COPD patients compared with the decreased levels in the blood plasma of patients with bronchial asthma and asthma-COPD overlap syndrome, whereas inversely, miR-125b was decreased in the blood plasma of COPD patients whereas increased in patients with bronchial asthma and asthma-COPD overlap syndrome. In addition, miR-320c was decreased in the blood plasma of patients with bronchial asthma, whereas upregulated in COPD patients with bronchial asthma and asthma-COPD overlap syndrome. The receiver operating characteristic curve (ROC) of patients with bronchial asthma for miR-19b, patients with asthma-COPD overlap syndrome for miR-125b, and COPD patients for miR-320c displayed an area under curve (AUC) of 0.824, 0.825, and 0.855, respectively.

In their case-control study, Wang *et al.* [81] measured the plasma levels of miR-126 in 70 acute exacerbation COPD patients, and 70 stable COPD patients. The levels of miR-126 were higher in acute exacerbation COPD patients than in stable COPD patients, showing an AUC of 0.805. Plasma miR-126 positively significantly correlated with GOLD stages in both patient cohorts. Furthermore, miR-126 levels were associated with those of TNF-α, IL-1β, IL-6 and IL-17 in acute exacerbation COPD patients, whereas the levels of miR-126 only positively correlated with TNF-α and IL-17 levels in stable COPD patients.

Ding *et al.* [84] analyzed the plasma levels of miR-150 in 59 COPD patients which were significantly lower than those in the healthy control group. The expression levels were also lower in patients with a severe airflow limitation than patients with a mild limitation. Plasma levels of miR-150 are positively associated with pulmonary function indicators whereas negatively associated with the count of leukocytes and C-reactive protein levels. ROC revealed an AUC of 0.819, a sensitivity of 64.4% and a specificity of 92.3%, suggesting the predictive value of plasma miR-150 for COPD. A completive study was performed by Zhu *et al.* [83] who showed that lower plasma levels of miR-150 was associated with diagnosis, severity of the disease, and lung function. Exposure to cigarette smoke for 3 months or 3 days reduced the levels of miR-150 in plasma and lung tissue of mice. *In vitro*, miR-150 overexpression led to the decrease in the levels of inflammatory factors, such as interleukins (IL-6 and IL-8), cyclooxygenase-2 (COX-2), and endoplasmic reticulum (ER) stress markers, glucose-regulated protein (GRP) 78 and C/-EBP homologous protein (CHOP), promoting cell migration. Systematically, miR-150 displayed binding activity to the 3′-untranslated region (3´UTR) of inositol requiring enzyme 1α (IRE1α), whereas IRE1α overexpression effaced the impact of miR-150. In lung tissues of mice, miR-150 overexpression antagonized IRE1α upregulation triggered by cigarette smoke, inflammation, and ER stress.

As demonstrated by Shen *et al.* [85], the plasma levels of miR-196 and miR-361 were down and up-regulated in 20 COPD patients, respectively, compared with healthy controls. In bronchial epithelial cells, miR-196 and miR-361 targeted the 3'UTR RNA of the Rho guanine nucleotide exchange factor arhgef12, and the cell membrane protein abca1 involved in cholesterol transport, respectively. Phytosterine sitosterol significantly suppressed miR-196, whereas stimulated miR-361, and so, inhibited bronchial epithelial cells proliferation. Sitosterol-promoted miR-361 expression inhibited the transaminase BCAT1 and declined the mTOR-pS6K pathway, leading to an anti-proliferation of bronchial epithelial cells. Due to the repressive effect of miR-196 on ARHGEF12 3'UTR that was partially abolished by sitosterol that suppressed miR-196-5p expression, RhoA was activated by ARHGEF12 which in turn activated ROCK1-PTEN pathway and consequently hindered mTOR pathway, mediating an induced bronchial epithelial cells proliferation.

Plasma of 36 COPD patients were collected by Zhang *et al.* [90]. Analysis of miR-423-5p showed an AUC of 0.9651 for the diagnosis of COPD, while the levels was inversely associated with the duration of smoking.

In the plasma of 40 Tibetan COPD patients, Shi *et al.* [78] screened a total of 210 differentially expressed miRNAs, and found that the combination of plasma miR-106, miR-486 and the mRNA expression of surfactant protein D (SP-D) played a role in the immune defense, and was the best model to assist the diagnosis of Tibetan COPD.

Club cell secretory protein (CC16) is the most abundant protein in bronchoalveolar lavage fluid. In smoke-exposed lungs, CC16 has anti-inflammatory properties and plays a role in oxidation [109]. However, COPD patients only display low levels of CC6 in their blood circulation, resulting in progressive lung damage. In mice, CC16 deficiency has been reported to increase smoke-induced lung pathologies, affecting epithelial cells, leukocytes, and fibroblasts [110]. Eckhardt *et al.* detected 22 miRNAs in exosomes which correlated with serum levels of CC16, suggesting that exosomal miRNAs plays an essential role in the pathway associating CC16 to COPD pathogenesis, while they control inflammation, immunity, and structural integrity in the lung [111]. Carpi *et al.* [56] detected the presence of miR-191 in exosomes derived from peripheral blood of COPD patients and found a relationship of

miR-191 levels with inflammatory parameters. When they incubated bronchial epithelial cells with exosomes containing miR-191, the NF-kB signaling pathway was activated along with an increase in the synthesis of IL-8. These findings show that miR-191 transported by exosomes plays a role in airway inflammation. It may support the pathogenesis of COPD by propagating inflammation by exome shuttle from cell to cell.

Using a miRCURY LNA miRNA serum/plasma assay, specific for 179 miRNA targets, O´Farrell *et al.* [57] analyzed the miRNA expression in plasma exosomes of 20 exacerbating and 20 stable COPD participants with different GOLD stages. Exosomal miR-374b was significantly dysregulated in COPD patients with moderate GOLD compared to those with severe or very severe GOLD, demonstrating an AUC of 0.798. Moreover, five miRNAs could significantly distinguish between exacerbating and stable COPD participants, in particular miR-223 with an AUC of 0.755. A combination of 3 miRNAs (miR-92b, miR-374a and miR-106b) provided the highest discriminatory power with an AUC of 0.820.

Using a microarray, Hu *et al.* [75] detected dysregulated levels of miRNAs in bronchial alveolar lavage cells and plasma of 12 COPD patients and 7 community-acquired pneumonia (CAP) patients. In the miRNAs target pathway networks, miR26/ and miR-3529/CDC42/MAPK signaling pathway may play an important role in the development of COPD by affecting inflammatory and oxidative stress.

6.2. Analyzed extracellular lncRNAs in COPD

In addition, lncRNAs have also been detected in COPD patients [112]. However, there are fewer studies that have dealt on extracellular lncRNAs in COPD patients. Table 2 gives a summary of studies on deregulated extracellular lncRNAs and their targets detected in COPD. As shown in this table, lncRNAs mainly interact with miRNAs, and so, inhibit the inhibitory function of miRNAs on the expression of mRNAs.

In the following, some examples of studies on extracellular lncRNAs in COPD are described in more detail:

In their study, Liu *et al.* [113] analyzed plasma from 120 acute exacerbation COPD (AECOPD) patients and 120 stable COPD patients. The plasma levels of lncRNA MALAT1 were significantly higher in AECOPD than in stable COPD patients which in turn were higher than in healthy individuals. The difference in these plasma levels between AECOPD patients and stable COPD patients displayed an AUC of 0.846. Furthermore, lncRNA MALAT1 was associated with GOLD staging, TNF-α, IL-1β, IL-6, IL-8, IL-17, and IL-23 in both AECOPD and stable COPD patients. In addition, lncRNA MALAT1 inhibited miR-125b, miR-146a, and miR-203 in AECOPD patients, while it inhibited miR-125b and miR-146a in stable COPD patients, leading to inflammation in AECOPD and stable COPD patients.

As shown by Chen *et al.* [114], the expression of lncRNA SNHG4 decreased in the serum of 50 COPD patients. They were lower in AECOPD than those in stable COPD patients. The reduced expression of SNHG4 caused that histon-lysin-N-methyltransferase (EZH2), a downstream target gene of miR-144 was also decreased, promoting the progression of COPD by reducing the viability, and stimulating apoptosis and inflammatory response of bronchial epithelial cells.

Zhao *et al.* [115] found that lncRNA LUCAT1 was upregulated in the serum of 70 COPD patients, and detected a significant correlation between LUCAT1 expression and IL-1β, IL-6, and TNF-α. Mechanically, rescue assays demonstrated that LUCAT1 regulated cigarette smoke extract-induced cell

proliferation and apoptosis by targeting miR-181a within the Wnt/β-catenin pathway. Conversely, miR-181a had also a feedback effect on LUCAT1.

Table 2. Deregulated extracellular lncRNAs detected in COPD.

lncRNAs	Targets	Correlations*	Source	Ref.
MALAT1	miR-125b, miR-146a, miR-203	TNF-α, IL-1β, IL-6, IL-8, IL-17, IL-23	Plasma	[113]
ANRIL		TNF-α, IL-1β, IL-8, IL-17A, LTB-4	Plasma	[116]
XIST			Serum	[117]
SNHG4	miR-144	EZH2	Serum	[114]
IL7R		p16, p21	Serum	[118]
OIP5-AS1	miR-410	IL-13	Serum	[119]
CASC2	miR-18a	IGF1	Serum	[120]
LUCAT1	miR-181a	Wnt/β-catenin	Serum	[115]
PACER		PPA	Serum	[121]
PVT1	miR-146a	TNF-α, IL-6, IL-8, IL-17	Serum	[122]

*Correlations refer to cytokines, signaling pathways. Abbreviations are mentioned below Table 1.

Cohorts of 80 AECOPD patients and 80 stable COPD patients were recruited by Wang *et al.* [122]. The serum levels of lncRNA PVT1 were highest in AECOPD patients, followed by stable COPD patients and healthy controls. The serum levels distinguished between AECOPD patients, stable COPD patients and healthy controls. A positive correlation of lnc-PVT1 expression with the GOLD stage and levels of TNF-α, IL-6, IL-8, and IL-17 was noticed in both patient groups. Moreover, lnc-PVT1 was negatively associated with miR-146a, whose expression was lowest in AECOPD patients, followed by stable COPD patients and healthy controls.

6.3. Analyzed extracellular circRNAs in COPD

A few studies were only performed on extracellular circRNAs in COPD patients [123]. Table 3 gives a summary of these studies on deregulated extracellular circRNAs and their targets detected in COPD. As shown in this table, circRNAs preferentially bind to miRNAs to exert their ceRNA activity.

Table 3. Deregulated extracellular circRNAs detected in COPD.

circRNAs	Targets	Correlations	Source	Ref.
circ_0062683, circ_0089763, circ_0008882	miR-612, miR-593, miR-765, miR-103a		Plasma	[70]
circ_0040929	miR-515	IGFBP3	Serum, exosomes	[71]
circ_RMRP, circ_RPL27			Serum	[124]

*Correlations refer to cytokines, signalling pathways. Abbreviations are mentioned below Table 1.

In their study, Tang *et al.* [70] screened the differential expression of 90 upregulated and 29 downregulated circRNAs in plasma of 30 COPD patients with a very severe disease using microarray technology. Plasma circ_0062683 was significantly upregulated, whereas circ_0089763 and circ_0008882 were downregulated. The construction of a circRNA-miRNA interaction network revealed that miR-103a,

miR-612, miR-593 and miR-765 were regulated by the differentially expressed circRNAs, participating in the development of COPD through hypoxia and the regulation of various immune cells.

As demonstrated by Miao *et al.* [71], the serum levels of circ_0040929 and insulin-like growth factor binding protein 3 (IGFBP3) expression were upregulated in 22 smokers compared with 22 non-smokers, and more significantly upregulated in 22 COPD patients. MiR-515 was revealed to be a direct target of circ_0040929, while IGFBP3 was a target of miR-515. Consequently, circ_0040929 regulated IGFBP3 expression by targeting miR-515. High levels of circ_0040929 were also detected in serum exosomes derived from COPD patients.

The potential of circ_RMRP and circ_RPL27 as biomarkers for COPD was investigated by Li *et al.* [124]. Due to the lung function, 50 COPD patients were grouped into mild, moderate, and severe disease subgroups. The serum levels of circ_RMRP and circ_RPL27 were increased in COPD patients and augmented with the severity of COPD. Both circ-RNAs referred to smoking history.

7. Treatment of COPD patients

In clinical practice, treatment strategies of COPD follow the recommendations of GOLD. Typically, bronchodilators, such as long-acting β2 agonists (LABA) and long-acting muscarinic antagonist (LAMA), together with anti-inflammatory agents, such as corticosteroids, are mainly used for COPD patients. In addition, a new bifunctional dimer molecule muscarinic antagonist/beta2-agonist (MABAs) advances the bronchodilator groups of molecules.

Chronic inflammation in the airways is associated with a higher number of lymphocytes and dendritic cells. Cytokines, including interleukins and TNF-α, and chemokines, including CXCL8, are involved in the pathology of COPD. These inflammatory molecules may be potential targets to avoid recruitment and stimulation of inflammatory cells and mediators in the pathogenesis of COPD.

In this respect, a pre-clinical study performed by Castro *et al.* [125] showed that airway inflammation in mice exposed to tobacco smoke was prevented after carrying out a treatment with an anti-IL-1β monoclonal antibody. In a TNF receptor knockout mouse model, Churg *et al.* [126] indicated that TNF-α may amount to 70% of smoke-induced emphysema. Stimulation of TNF receptor induced synthesis and release of cytokines (e.g., TNF-α, IL-1), chemokines (e.g., CXCL-8, MCP-1), and proteases (e.g., MMP-9, MMP-12). However, although TNF-α inhibitors have a synergistic effect with corticosteroids in monitoring airway remodeling and recovering corticosteroids insensitivity, their inhibitors have reported to display reduced clinical efficiency in the management of COPD [127]. In a preclinical study on a murine model of LPS-induced lung inflammation, Fiorentini *et al.* [128] showed that modified recombinant human CXCL8 with increased glycosaminoglycan binding reduced bronchoalveolar lavage neutrophils and systemic inflammatory markers. Using a dose-ranging proof of concept trial, Rennard *et al.* [129] found that treatment with a CXCR2 receptor antagonist led to a significant improvement in forced expiratory volume. Nevertheless, dose-related discontinuations were observed because the absolute neutrophilic count was decreased.

As detailed described by Yadav *et al.* [3], a lot of studies have failed to accomplish a substantial clinical benefit for COPD patients or improvements of this disease. Therefore, new therapy strategies are necessary to stop the progression of COPD. Target molecules for COPD treatment could be ncRNAs, such as miRNAs, lncRNAs and circRNAs, since a variety of these ncRNAs are pivotal contributors to the pathology of COPD. However, the development of RNA-based drugs for COPD treatment are still

in its infancy. The major obstacle in using RNA therapies for COPD patients is due to achieve effective and specific delivery systems. Because of its minimal patient inconvenience, pulmonary delivery of inhaled RNA drugs is preferred. However, prior to reaching their intended therapeutic targets, inhaled drugs may interfere endogenous lung substances and various lung cell types.

So far, a very few pre-clinical trials have only been carried out on miRNAs in COPD (ClinicalTrials.gov, NIH). However, they are still incomplete or do not show any results. Thus, the future will disclose whether ncRNAs are useful targets in the therapy of COPD.

8. Discussion of the potential pathogenicity of deregulated ncRNAs

An increasing number of studies has recognized the functional roles of ncRNAs in variety of biological processes and their deregulation in a variety of benign and malignant diseases [9]. They may be potential disease biomarkers and targets for therapies. It is assumed that there is a relationship between disease and altered expression levels of ncRNAs. In this respect, the relationship of various ncRNAs with lung diseases has been reported [130]. For example, miR-26a is expressed in murine bronchial and alveolar epithelial cells, and binds to the transcription factor SMAD-1 which plays a critical role in the lung development process [131]. During early lung embryogenesis, the miR17-92 cluster is highly expressed, while its levels decrease throughout development. Overexpression of this miRNA cluster leads to deregulated cell proliferation [132]. MiR-155 contributes to lung immunity. Immune deficient mice fail to immunologically response to exogenous stimuli [133]. At the initiation of inflammation, miR-146a and miR-146b, those levels are increased in the serum of COPD, are involved in IL-1β activity. Overexpression of these miRNAs mediates downregulation of TNF-α and various proinflammatory cytokines [102].

Diagnosis of COPD increases the risk of lung cancer, mediated by inflammatory processes [134]. Therefore, a further question arises whether changes in the expression of certain ncRNAs can contribute to this increased risk in COPD patients. For example, miR-17-92 and let-7 in COPD have been reported to be linked with lung carcinogenesis [135,136].

9. Conclusion

Numerous studies, as described above, have shown that ncRNAs significantly contribute to the pathophysiology of COPD and affect the expression of target mRNAs in the inflammatory network of COPD, modulating several signaling pathways. Their dysregulation is associated with the dynamic of the disease course and progression of COPD. Therefore, the use of ncRNAs as biomarkers or in therapies could possibly be promising for COPD patients. However, the hitherto existing studies are assorted and have many shortcomings. They use relatively small, heterogenous patient cohorts, different tissue samples, and different techniques. In addition, the interplay between ncRNAs should be considered because of their function as ceRNAs and their interference among each other. In this respect, one ncRNA can sponge several ncRNAs and inversely, several ncRNAs can sponge one ncRNA. In addition, the ability of ncRNAs to interact with several mRNA targets should be reviewed. Based on this complex interplay, biological network models in which miRNAs, lncRNAs and circRNAs and other ncRNAs are integrated have to be designed to better understand their modulating impact on the different signaling pathways in COPD. Therefore, multicenter studies are absolutely necessary to analyze the potential clinical significance of ncRNAs in the course of the disease.

To apply ncRNAs in clinical treatment strategies, ncRNA mimics or inhibitors with a high specificity have to be created and transferred in improved delivery systems to the inflammatory site of the lung, to abrogate the adverse effect of ncRNAs in COPD. New delivery possibilities include exosomes modified with specific surface marker to pilot them to the hot spot of inflammatory lung.

In summary, deciphering of the regulatory network of ncRNAs remains an essential undertaking for the future to develop effective therapeutic agents and to inhibit COPD progression.

Conflicts of interests

The author discloses any potential conflict(s) of interest like employment, consulting fees, research contracts, stock ownership, patent licenses, honoraria, advisory affiliations *etc*.

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