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Review

The roles of microRNAs in the pathogenesis of chronic obstructive pulmonary disease

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) is characterized by a progressive and irreversible airflow obstruction, with an abnormal lung function. The etiology of COPD correlates with complex interactions between environmental and genetic determinants. However, the exact pathogenesis of COPD is obscure although it involves multiple aspects including oxidative stress, imbalance between proteolytic and anti-proteolytic activity, immunity and inflammation, apoptosis, and repair and destruction in both airways and lungs. Many genes have been demonstrated to be involved in those pathogenic processes of this disease in patients exposed to harmful environmental factors. Previous reports have investigated promising microRNAs (miRNAs) to disclose the molecular mechanisms for COPD development induced by different environmental exposure and genetic predisposition encounter, and find some potential miRNA biomarkers for early diagnosis and treatment targets of COPD. In this review, we summarized the expression profiles of the reported miRNAs from studies of COPD associated with environmental risk factors including cigarette smoking and air pollution exposures, and provided an overview of roles of those miRNAs in the pathogenesis of the disease. We also highlighted the potential utility and limitations of miRNAs serving as diagnostic biomarkers and therapeutic targets for COPD.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by a progressive and irreversible airflow limitation, with an abnormal lung function [1]. Its pathology consists of two distinctly and frequently coexisting aspects including small airway obstruction and destruction of lung parenchyma, with strong contribution heterogeneity among patients and within the lung [2]. At present, at least several mechanisms are thought to be involved in the pathogenesis of COPD, including the imbalance between proteolytic and anti-proteolytic activity, influx of inflammatory cells into the lung, oxidative stress, and the imbalance between apoptosis and replenishment of structural cells in the lung [3], and multiple signaling pathways are involved in those mechanisms. Many genes associated with these signaling pathways have been demonstrated to play important roles in COPD development, including apoptotic and autophagic responses of the lung, cellular differentiation and survival, endothelial cell proliferation, airway inflammation, and antiviral response and impaired lung function (Table 1 and Table 2).

COPD is a multifactorial disease caused by environmental and genetic risk factors. Cigarette smoking (CS) and indoor and outdoor air pollution exposure are main environmental pathogenic factors [4]. While large-scale genome-wide association studies (GWAS) have identified many single nucleotide polymorphisms (SNPs) associated with COPD susceptibility [5]. However, most of those SNPs are located in non-coding regions of the potentially predisposing genes. Thus, the causal effects of the susceptibility alleles may trace back to the regulatory malfunction of the non-coding regions in the genes. Although many signaling pathways have been identified in the pathogenesis of COPD [6–8], how the genes involved in the pathways interplay with different environmental exposures in COPD development remains obscure.

MicroRNAs (miRNAs) are a group of small non-coding RNAs (approximately 22 nucleotides in length) and key modulators in multiple biological pathways involved in cell proliferation and differentiation, development and apoptosis [9]. MiRNAs are highly conserved throughout evolution. One study demonstrated that more than 5300 genes have putative miRNA target sites and one gene also can be targeted by multiple miRNAs [10]. A single miRNA can bind to hundreds of messenger RNA targets resulting in their degradation or inhibition of translation [11]. Based on these assessments, one third of the human genome could be prone to post-transcriptional modulation by miRNAs [12]. Additionally, dysregulated miRNAs have been identified in lung

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Table 1
The microRNAs involved in pathogenesis of COPD.

MicroRNA type	Identified/potentially targeted genes	Findings	Validating methods	References
miR-210	*MKP-1*	Inhibiting miR-210 expression increased *MKP-1* mRNA and protein expression in hPASMCs and decreased cell proliferation under hypoxia	qRT-PCR, western blot analysis	[49]
miR-199a-5p	*HIF-1a*	The increased expression of miR-34a and miR-199a-5p was observed in patients with COPD/emphysema, and was associated with impaired lung function, as assessed by FEV1% predicted, and may also affect the HIF-1a-dependent lung structure maintenance program.	qRT-PCR, western blot analysis	[24]
miR-15b	*SMAD7*	miR-15b targets *SMAD7* in bronchial epithelial cells and alters *TGF-B* signaling	mRNA and miRNA microarray, qRT-PCR	[43]
miR-146a	*COX-2*	The expression of miR-146a assessed showed significant negative correlation with *PGE2* production following cytokine stimulation, and was also significantly correlated with COPD severity assessed by FEV1 and DLCO. miR-146a may modulate *COX-2* and *PGE2* production in COPD Fibroblasts.	qRT-PCR, western blot analysis, bioinformatic analysis	[46]
let-7c	*TNFR2*	One of the let-7c targets is *TNFR2* that is involved in the pathogenesis of the COPD, and reduced expression of let-7c increases the expression of *TNFR2*. Reduced expression of let-7c could indicate an inflammatory and progressive state of COPD.		[18,40]
miR-101 and miR-144	*CFTR*	Up-regulation of miR- 101 and/or miR144 could contribute to the suppression of *CFTR* observed in COPD patients	qRT-PCR, immunohistochemistry	[25]
miR-101	*MKP-1*	miR-101 regulates the innate immune responses of macrophages through targeting MKP-1	qRT-PCR, small interfering RNA, Western blot and immunoprecipitation	[80]
miR-483-5p		miR-483-5p, which was significantly downregulated in COPD samples, abrogated the transforming growth factorβ mediated decrease in cell proliferation, and increase in αsmooth muscle actin and fibronectin expression in pulmonary epithelial and lung fibroblast cell lines.	miRNA microarray, qRT-PCR	[22]
miR-196a2	*PDGFRA*, *ROCK1*, *OCRL*,*DIAPH2*, *GSTP1*, *ACE*, *HTR4*, *PPT2*, *THSD4*, *COL3A1*, *COL1A1*, *COL1A2*, *PDGFRA*, *EPB41L2*,*CASK*,*HOXA5*,*HOXA7*,*HOXB6*,*HOXB8*, *and HOXC8*	miR-196a2 rs11614913 polymorphism was showed to be related to the bronchodilator response of COPD in the Egyptian population and COPD risk.	SNP Genotyping, in silico target prediction and network core analysis	[9,48]
miR-21		miR-21 could increase autophagy and promote the apoptosis of 16HBE cells in COPD	qRT-PCR, immunohistochemical staining	[26]
miR-34a	*Notch-1*	miR-34a plays a key role in CSE-induced endothelial cell apoptosis by directly regulating its target gene Notch-1 in endothelial cells	qRT-PCR, western blot analysis	[32]
miR-195	*PHLPP2*	miR-195 has a pathogenetic role in CS-induced COPD and regulates Akt signaling by suppressing PHLPP2 expression.	qRT-PCR, western blot analysis	[15]
miR-150	*p53*	miR-150 suppresses CS-induced lung inflammation and airway epithelial cell apoptosis, which is causally linked to repression of p53 expression and NF-B activity	qRT-PCR, western blot analysis	[27]
miR-503	*VEGF*	Reduced miR-503 augments VEGF release from lung fibroblasts from patients with COPD. Altered miR-503 production might play a role in modulating fibroblast-mediated vascular homeostasis in COPD. MiR-503 expression was positively correlated with lung function	Luciferase assay, qRT-PCR	[28]
miR-218	*TNFR1*	miR-218 regulates CSE-induced MUC5AC hyper-production and inflammation by targeting TNFR1- mediated activation of NF-κB. miR-218 significantly associated with chronic obstruction and severity.	CRISPR 9, qRT-PCR, western blot analysis	[19,52]
miR-181c	*CCN1*	miR-181c over-expression alleviated lung injury in COPD, as evident from the resulting amelioration of lung injury, reduction of the inflammatory response, neutrophil infiltration, and ROS generation, and downregulation of CCN1 expression	qRT-PCR, immunosorbent assay	[21]

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Table 1 (*continued*)

MicroRNA type	Identified/potentially targeted genes	Findings	Validating methods	References
miR-214	*PTEN*	miR-214 signifcantly promotes the proliferation of pulmonary artery smooth muscle cells by suppressing apoptosis of the cells, which is mediated by the downregulation of PTEN.	qRT-PCR, immunohistochemistry, and Western blot	[50]
miR-214	*EGFR*	*EGFR* acts as a target of miR-214 in pulmonary artery smooth muscle cell (PASMCs). Exogenous overexpression of miR-214 significantly downregulates the expression of *EGFR* in the PASMCs genotyped as TT or TC, but not in CC group.	Genotyping, qRT-PCR, luciferase assays	[50]
miR-34c	*SERPINE1*	MiR-34c modulates expression of its putative target gene, SERPINE1, in vitro in respiratory cell lines and ex vivo in emphysematous lung tissue.	mRNA microarrays, qRT-PCR	[44]
miR-149-3p	*TLR4*	Reducing miR-149-3p may increase the inflammatory response in COPD patients through the regulation of TLR4/NF-κB signaling	miRNA microarray,qRT-PCR, Western blot and immunofluorescence	[20]
miR-344b-1-3p	*TLR2*	miR-344b-1-3p inhibition increases the expression levels of *TLR2*, *TNF*-α, *and IL-1*β and decreases the expression levels of *MIP-2*	miRNA microarray,qRT-PCR, Western blot	[53]
miR-203	*TAK1* and *PIK3CA*	miR-203 represses NF-κB signaling via targeting *TAK1* and *PI3KCA* and miR-203 overexpression may contribute to the COPD initiation	qRT-PCR, Immunoblotting, luciferase assay and western blot	[16]
let-7 g	*KRAS*	*KRAS* 3′-UTR rs712 polymorphism interferes with miRNA/mRNA interaction, and the minor allele is associated with an elevated risk for development of lung cancer in COPD	Genotyping, qRT-PCR, western blot	[54]

qRT-PCR:Real-time RT-PCR and quantification.

Table 2
Summary of COPD-related genes validated as targets for microRNAs.

Gene	Chromosomal location	The role of gene in pathogenesis of COPD	Reference
Cystic fibrosis transmembrane conductance regulator (*CFTR*)	7q31.2	*CFTR* is a chloride channel that plays a critical role in maintaining fluid homeostasis in the lung. Reduced expression of *CFTR* could contribute to the development of COPD. *CFTR* regulates apoptotic and autophagic responses in CS-induced lung injury that may be involved in the pathogenesis of severe emphysema.	[25,79]
Mitogen-activated protein kinase phosphatase 1 (*MAPK-1*)	22q11.22	*MAPK-1* provides an important negative feedback loop in multiple cellular processes, including growth factor signaling, inflammation, differentiation, and apoptosis, by dephosphorylating mitogen-activated protein kinases. *MAPK-1* appears to control diverse functions in the hypoxic state such as chronic hypoxic caused by COPD?	[49]
Dual specificity phosphatase 1 (*MKP-1*)	5q35.1	*MKP-1* reverses the activation of MAPK family, induced by EGF, predominantly expressed in lung, placenta, pancreas, involved in signal transduction. *MKP-1* plays an important role in regulation of in airway inflammation, and involves clinical use of medicines of respiratory diseases including COPD.	[80,83]
Hypoxia-inducible factor-1a(*HIF-1a*)	14q23.2	*HIF-1a* functions as a master transcriptional regulator of the adaptive response to hypoxia. The expression of *HIF-1a* protein was reduced in lungs from patients with COPD and with varying degrees of lung function impairment.	[24]
SMAD family member 7 (*SMAD7*)	18q21.1	*SMAD7* inhibits TGF-beta and activin signaling by associating with their receptors thus preventing *SMAD2* access. Functions as an adapter to recruit *SMURF2* to the TGF-beta receptor complex. Expression of *SMAD7*, which was validated as a target for miR-15b, was decreased in bronchial epithelial cells in COPD.	[43]
Prostaglandin-endoperoxide synthase 2 (*COX-2*)	1q31.1	*COX-2* plays important roles in modulating motility, proliferation and resistance to apoptosis. Fibroblasts from patients with COPD underexpress miR-146a after stimulation with *IL-1b* and *TNF-a*, which leads to reduced degradation of *COX-2* mRNA and overproduction of *PGE2*.	[46]
Tumor necrosis factor receptor 2 (*TNFR2*)	1p36.22	*TNFR2* is involved in the pathogenesis of the COPD. *TNFR2* knock out inhibits inflammation and emphysema.	[40]
Notch (drosophila) homolog 1 (translocation-associated) (*Notch-1*)	9q34.3	*Notch-1* functions as a receptor for membrane-bound ligands Jagged1, Jagged2 and Delta1 to regulate cell-fate determination. It is a critical downstream target of miR-34a in regulating the CSE-induced HPMEC apoptosis.	[32]
PH domain and leucine rich repeat protein phosphatase 2 (*PHLPP2*)	16q22.2	*PHLPP2* mediates dephosphorylation in the C-terminal domain hydrophobic motif of members of the AGC Ser/Thr protein kinase family. Inhibition of PHLPP2 enhanced Akt phosphorylation and increased interleukin-6 and tumor necrosis factor-α production in BEAS-2B cells, resembling the effects of miR-195 overexpression.	[15]
Tumor protein P53 (*P53*)	17p13.1	*P53* acts as a tumor suppressor in many tumor types, induces growth arrest or apoptosis depending on the physiological circumstances and cell type, and is involved in cell cycle regulation as a trans-activator that acts to negatively regulate cell division by controlling a set of genes required for this process.	[27]
Vascular endothelial growth factor A (*VEGFA*)	6p21.1	*VEGFA* induces endothelial cell proliferation, promotes cell migration, inhibits apoptosis and induces permeabilization of blood vessels. VEGF is a potent growth factor essential for maintaining pulmonary vasculature, which is disturbed in COPD.	[28]
TNF receptor superfamily member 1A (*TNFR1*)	12p13.31	*TNFR1* is involved in acidic sphingomyelinase controlling expression of multiple TNF-responsive genes,including the apoptotic pathway, neutral sphingomyelinase critical for the inflammatory and proliferative responses. TNFR1 plays an important role in pathogenesis of cigarette smoke-induced COPD.	[52]
Cysteine rich angiogenic inducer 61 (*CCN1/CYR61*)	1p22.3	*CCN1* Promotes cell proliferation, chemotaxis, angiogenesis and cell adhesion, appears to play a role in wound healing by up-regulating, in skin fibroblasts, and is associated with pathogenesis of cigarette smoke-induced COPD.	[21]
Phosphatase and tensin homolog (*PTEN*)	10q23.31	*PTEN* modulates cell cycle progression and cell survival via the AKT signaling pathway, and is a negative regulator of cell interactions with the extracellular matrix, mutated in multiple advanced cancers. *PTEN* is identified as important risk factor of COPD and lung cancer.	[50]
Serpin family E member 1 (*SERPINE1*)	7q22.1	*SERPINE1* acts as bait for tissue plasminogen activator, urokinase, protein C and matriptase-3/TMPRSS7. Its rapid interaction with PLAT may function as a major control point in the regulation of fibrinolysis. *SERPINE1* is only one of a number of antiproteases, and has other roles in the lung that could be relevant to the progression of emphysema and COPD	[44]
Mitochondrial antiviral signaling protein (*MAVS*)	20p13	Mitochondrial MAVS acts sequentially to create an antiviral cellular state. Upon viral infection, peroxisomal *MAVS* induces the rapid interferon-independent expression of defense factors that provide short-term protection, whereas mitochondrial *MAVS* activates an interferon-dependent signaling pathway with delayed kinetics, which amplifies and stabilizes the antiviral response. *MAVS* protein levels were reduced in COPD and this in turn promotes NF-κB–induced inflammation and attenuates antiviral IFN production, respectively, increasing viral replication.	[23]
Toll like receptor 4 (*TLR-4*)	9q33.1	*TLR-4* specifically expressed in placenta, and on cells of the immune system binding directly to TLR2 and essential component of liposaccharides (LPS) receptor,inducing the LPS signaling pathway. Acute levels of cigarette smoke exhibited increased *TLR-4* expression and *TLR-4* signaling, through *MyD88* and *IRAK1*, which play a predominant role in matrix metalloproteinase 1 induction, and results in lipopolysaccharides-independent *TLR4* activation, leading to *IL-1* production and *IL-1R1* signaling, which is crucial for cigarette smoke-induced inflammation leading to COPD with emphysema.	[20]
Toll like receptor 2 (*TLR2*)	4q31.3	*TLR2* might play an important role in the defense against IPA. The downexpression of *TLR2* in AMs contributed to the reduced TNF-α, IL-1β, and MIP-2 expressions in COPD AMs.	[53]

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Table 2 (*continued*)

Gene	Chromosomal location	The role of gene in pathogenesis of COPD	Reference
Mitogen-activated protein kinase kinase kinase 7 (*TAK1/MAP3K7*)	6q15	*TAK1* Plays an important role in the cascades of cellular responses evoked by changes in the environment, and mediates signal transduction of *TRAF6*, various cytokines including interleukin-1 (*IL-1*), transforming growth factor-beta (*TGFB*), TGFB-related factors like BMP2 and BMP4, toll-like receptors (TLR), tumor necrosis factor receptor CD40 and B-cell receptor.	[16]
Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (*PIK3CA*)	3q26.32	*PIK3CA* is required for lymphatic vasculature development, possibly by binding to RAS and by activation by EGF and FGF2, but not by PDGF, and regulates invadopodia formation through the PDPK1-AKT1 pathway, also participates in cardiomyogenesis in embryonic stem cells by an AKT1 pathway. It aslo involves vasculogenesis in embryonic stem cells through PDK1 and protein kinase C pathway.	[16]
KRAS proto-oncogene, GTPase (*KRAS*)	12p12.1	*KRAS* plays an important role in the regulation of cell proliferation and in promoting oncogenic events by inducing transcriptional silencing of tumor suppressor genes. COPD patients with GG genotype at rs712 within *KRAS* have significantly higher risk for lung cancer, compared with TT and GT genotypes.	[54]
Epidermal growth factor receptor (*EGFR*)	7p11.2	Receptor tyrosine kinase binding ligands of the EGF family and activating several signaling cascades to convert extracellular cues into appropriate cellular responses. It activates at least 4 major downstream signaling cascades including the RAS-RAF-MEK-ERK, PI3 kinase-AKT, PLCgamma-PKC and STATs modules, and also activates the NF-kappa-B signaling cascade. The dysregulation of *EGFR* has also been proposed to be responsible for the abnormal proliferation of PASMCs and development of pulmonary artery remodelin.	[51]
Glutathione S-transferase p1(*GSTP1*)	11q13.2	They are involved in cell-to-cell signaling, immune cell trafficking, and inflammation	[9]
Angiotensin I converting enzyme (*ACE*)	17q23.3		
5-hydroxytryptamine (*HTR4*)	5q32		
Palmitoyl-protein thioesterase 2 (*PPT2*)	6p21.32		
Thrombospondin, type I, domain containing 4 (*THSD4*)	15q23		

Information of genes is from HGNC (https://www.genenames.org/) and GeneCards (http://www.genecards.org/).

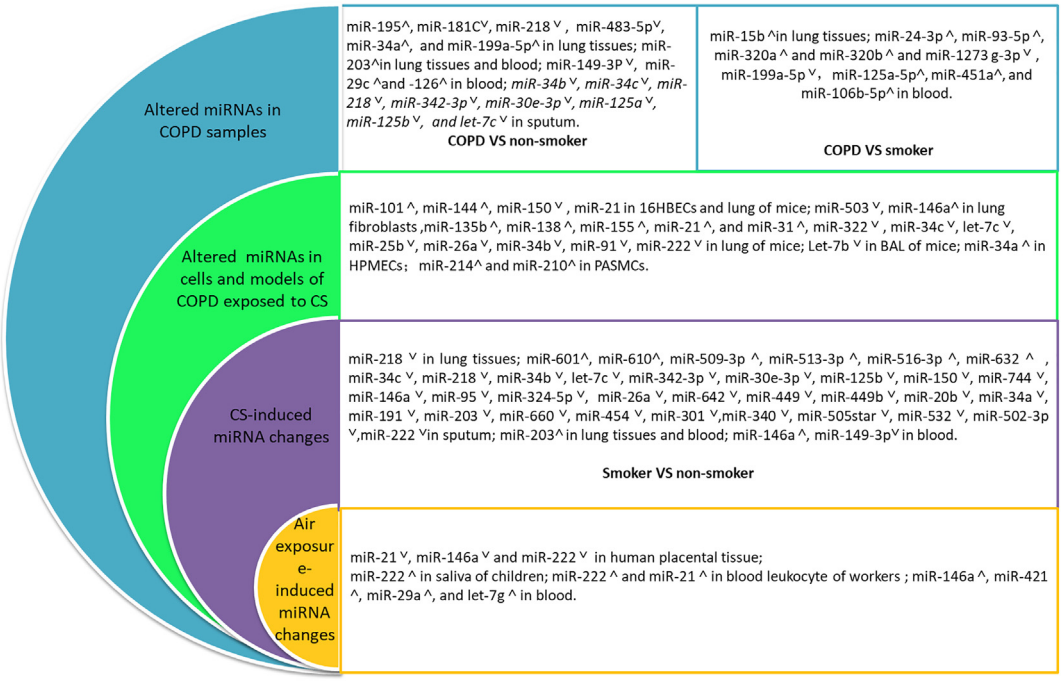

Fig. 1. miRNA expression profiles of COPD samples including COPD VS non-smoker and COPD VS smoker, in cells and models of COPD exposed to cigarette smoke (CS), health smokers, and human samples exposed to air pollution. ^ represents upregulation of miRNAs, while ˅ represents downregulation of miRNAs.

tissues and other body fluids in COPD including plasma, serum, sputum, bronchial lavage saliva, and pleural fluid [13–15]. Growing evidence demonstrated that miRNAs have the potential of being used as biomarkers for COPD. Exploration of dysregulated expression profile of miRNAs in distinct samples from COPD patients or model animals under different environmental exposures could be helpful for elucidating the role of miRNAs in the pathogenesis of COPD. Here we provided an overview of the interplay of those miRNAs with genetic predisposition and environmental risk factors of this disease. We also highlight the potential utility and limitations of miRNAs serving as diagnostic biomarkers and therapeutic targets for COPD.

2. The expression status of miRNAs in different COPD samples with distinct environmental exposures

Cigarette smoke exposure (CSE) is a main risk factor of COPD and

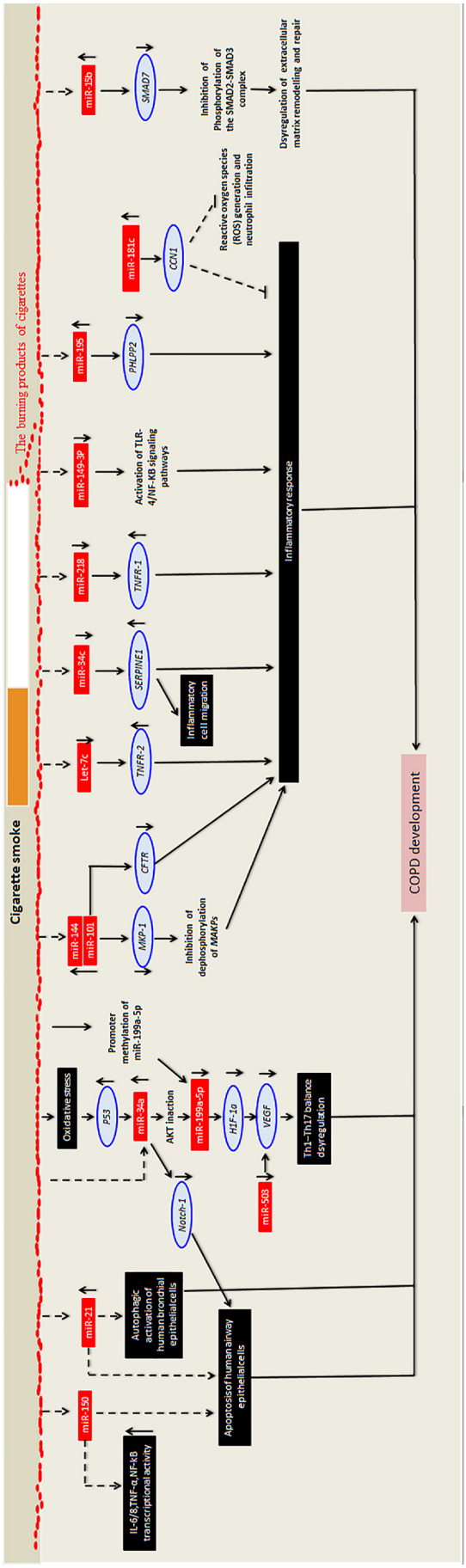

Fig. 2. Cigarette smoke induced miRNA-mediated regulation mechanisms for chronic obstructive pulmonary disease. Cigarette smoke (CS) induces dysregulation of some miRNA, which disturbs COPD-related gene expression levels, thus affecting signaling pathways involved in apoptosis, inflammatory response, oxidative stress, and extracellular matrix remodelling and repair in the airway epithelial cells. Dotted line represents indirect regulative role.

leads to aberrant expression of many miRNAs and COPD-related genes that are involved in multiple aspects of COPD pathogenesis. In a growing number of studies, differentially expressed miRNAs associated with chemical stimulation of tobacco and COPD pathogenesis were reported. As shown in Fig. 1, cigarette smoking can lead to upregulation of miR-203 in lung tissues [16], miR-146a in blood [17], and miR-601, -610, -509-3p, -513-3p, -516-3p, and -632 in sputum [18], while downregulation of miR-218 in lung tissues [19], miR-34c, -218, -34b, -125b, -146a, -34a, -222, and let-7c,etc. in sputum [18], and miR-149-3p in blood [20]. Those samples were from smokers without airway limitation. In previous case-control studies (COPD VS non-smokers and COPD VS smokers), many differentially expressed miRNAs, including miR-195, -181c, -218, -483-5p, -203, -29c, -126, -149-3P, -34b, -34c, -342-3p, -30e-3p, -125b, -125a-5p, -146a, -451a, -106b-5p, -34a, -199a-5p, and let-7c, were identified in a variety of samples from COPD patients, including lung tissues, sputum, and blood [15–24]. Furthermore, some of those aberrantly expressed miRNAs identified in studies of clinical samples were also found to have the consistent expression trends with those in vitro studies [1,25–32].

Although CS is the major risk factor for COPD, indoor and outdoor air pollution is also an important cause of pulmonary diseases including COPD [4,33]. Whereas the pathologic effects in the lung caused by air pollution are mediated through inflammatory pathways and oxidative stresses, which is similar to CS [34], air pollution-induced COPD differs from CS-induced COPD with respect to its disproportionately greater bronchial involvement, greater impact on quality of life, possibly greater oxygen desaturation, and lesser emphysematous change [33]. Therefore, the mechanism of differentially clinical manifestation needs to be clarified. In a growing number of studies, many miRNAs have been found to be involved in air pollution-induced COPD pathogenesis. MiRNA-21, -146a, and -222 were significantly downregulated in human placental tissue [35,36], while miR-146a, -421, -29a, -21, -222, and let-7g were found to be upregulated in adult blood [37,38], and expression of miRNA-222 was also increased in saliva of children under air pollution exposure [39]. Of which, the expressed trend of miRNA-146a and -222 was contrarily presented between fetus and adult samples, suggesting a possibility that cumulative air pollution may lead to miRNA-146a and -222 changes.

Among the above, expression of miR-218 and -203 were overlapped in smokers and COPD population, as well as miR-34 family (-34a/b/c), let-7 c, and 146a were overlapped in COPD patients and air pollution/CS-exposed population in mice, suggesting a potential of those miRNAs to serve as biomarker for COPD risk in susceptible individuals with environmental exposure.

3. The roles of miRNAs in the pathological process of COPD with environmental exposure

Environmental risk factors, mainly including cigarette smoke and indoor and outdoor air pollution, have an important role in the pathogenesis of COPD [40,41]. In in vitro studies (Table 1), many functional miRNAs including miR-1, -15b, -21, 34a/c, -101, -125a/b, -133, -144, -146a, -149-3p, -150, -181c, -183, -195, -196a2, -199a-5p, -203, -210, -214, -218, -344b-1-3p, -422a, -483-5p, and let-7c/g, etc. were identified that interact with COPD-related genes involved in COPD pathogenesis triggered by CSE and air pollutants [9,13,15,16,18–27,32,40,42–54]. Those functional genes and miRNAs mainly relate to *TGF*-β, focal adhesion, and Wnt pathways that are involved in the mechanisms of COPD including inflammatory response, imbalance between proteolytic and anti-proteolytic activity, oxidative stress, and apoptosis [3]. Although environmental changes can dysregulate miRNA and functional gene expression [55–57], however, their functional roles in COPD development induced by environmental exposures remain to be clarified.

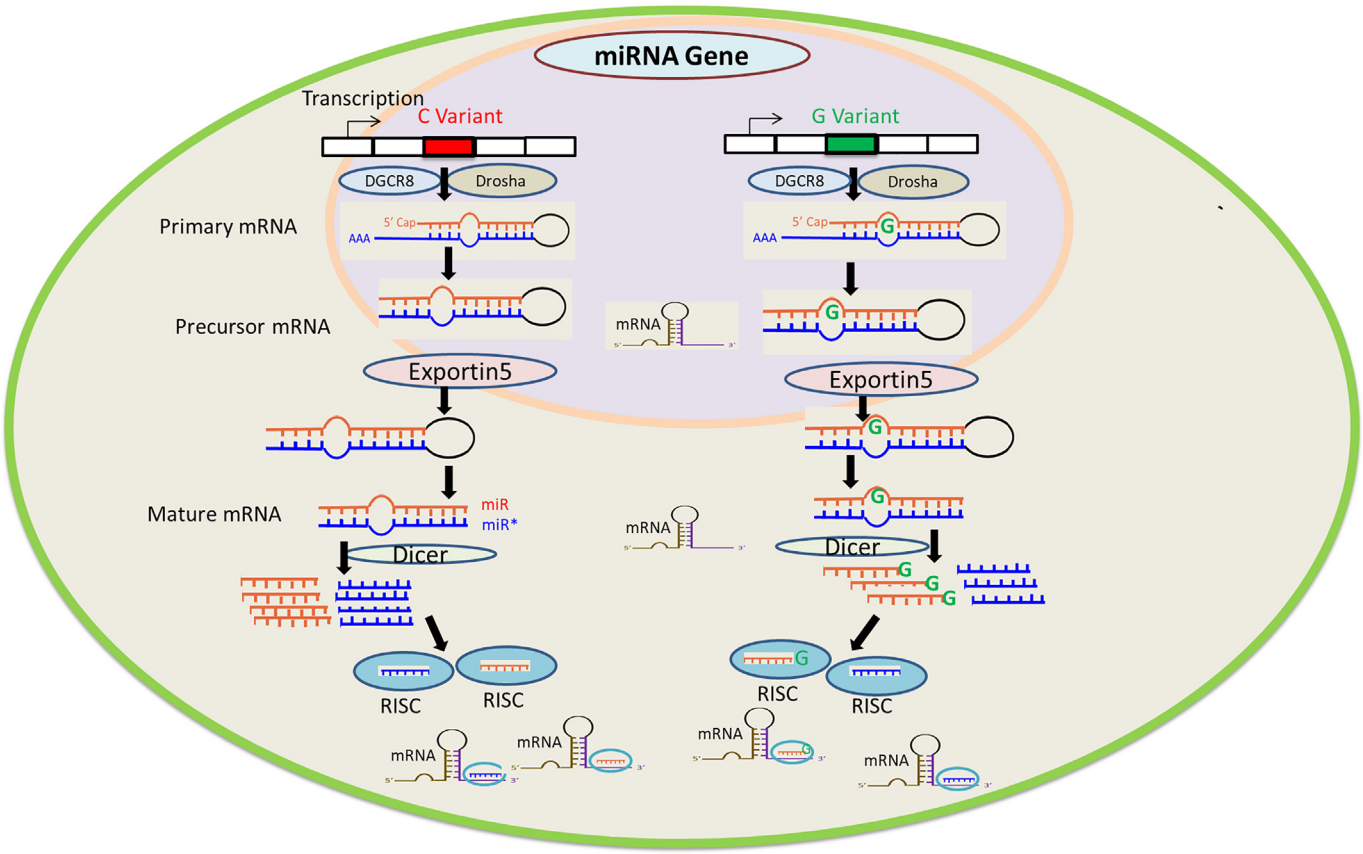

Fig. 3. Predicted functional impact of miRNA gene variant. After the transcription of the primary miRNA (pri-miRNA) transcript by RNA polymerase-II or -III, the precursor miRNA (pre-miRNA) is excised by DGCR8 and Drosha and then is transported into the cytoplasm by Exportin-5. Splicing of the pre-miRNA by Dicer generates the miRNA duplex consisting of two mature miRNA strands (miR and miR*), which together with some accessory proteins assembles into the RISC complex to control post-transcriptional modulation of target mRNA translation [12]. However, the functional single nucleotide polymorphism (SNP) variant (for example C converts to G) within some miRNAs might influence miRNA by affecting processing of the pre-miRNA to its mature form [127], and influence the regulative effects of miRNAs on mRNAs [116].

3.1. The role of miRNAs in the CS-induced regulatory changes of pathways involved in COPD development

3.1.1. The role of miRNAs in oxidative stress

Reactive oxygen and nitrogen species (ROS/RNS) have the capacity to serve as signaling moieties that participate in cell homeostasis [58]. Their accumulation within the cells might cause oxidative imbalances, altered homeostasis, as well as subsequent cell death [59]. Oxidative stress usually occurs when the production of the ROS, usually derived from the release of oxidants in the airways exposed to CS or in inflammatory leukocytes and epithelial cells, exceeds the level allowed by the antioxidant defense mechanisms [60]. Oxidative stress may cause multiple adverse events including cell dysfunction or cell death, damage of the lung extracellular matrix, and the proteinase-antiproteinase imbalance [3].

Additionally, oxidative stress may down-regulates Vascular Endothelial Growth Factor (VEGF) that is a potent growth factor controlling vasculature and often overexpresses in chronic inflammation [61], which is associated with decreased lung function [62] and apoptosis of pulmonary structural cells such as alveolar endothelial cells [3]. Furthermore, oxidative stress may enhance p53-mediated miR-34a expression, and subsequently inhibiting AKT activation by decreasing AKT phosphorylation, which upregulates miR-199a-5p level and reduces the expression of *HIF-1α*. Reduced expression of *HIF-1α* might suppress *VEGF* expression as well as phosphorylation of AKT, which could cause apoptosis of structural cells such as alveolar endothelial cells in the lung and contribute to the development of COPD/emphysema [3,24]. The inhibition of miR-199a-5p expression was observed to contribute to over-expression of bone morphogenic protein (BMP) signaling pathway/TGF-β, therefore may affects the regulation of the adaptive immune balance in favour of Th1 and Th17 cell responses, which is involved in COPD pathogenesis [63]. However, ROS resulted from CSE were found to produce continuously even after smoking cessation, and suppress miR-199a-5p expression via enhancing its promoter methylation [64,65]. Those findings may indicate that excessive ROS from CS leads to the suppression of the miR-199a-5p in susceptible individuals, and eventually contributing to COPD pathogenesis by dysregulating regulatory T cell (Treg)/Th1-Th17 balance. Furthermore, miR-503 was demonstrated to contribute to the pathogenesis of COPD and play an important role in vascular homeostasis in COPD, in which reduced miR-503 in COPD lung fibroblasts promotes VEGF release [28].

3.1.2. The role of miRNAs in apoptosis and replenishment of structural cells in the lung

In a number of in vivo and in vitro studies, apoptosis, which is associated with inflammation, proteinase-antiproteinase imbalance, and oxidative stress, has been identified having a vital role in the pathogenesis of COPD/emphysema [3]. CS can initiate apoptosis in various samples from COPD [66,67]. Low concentrations or short exposure time could induce cell apoptosis, while high concentrations or long exposure time could instead induce necrosis [68]. The exact mechanism of cell apoptosis in the pathogenesis of COPD with CSE is little known. However, some miRNAs have been demonstrated to play important roles in the imbalance between apoptosis and replenishment of structural cells in the lung exposed to CSE. The upregulation of miR-34a induced by

CSE was reported to induce apoptosis of human pulmonary microvascular endothelial cells (HPMECs) via inhibiting its target gene *Notch-1* [32]. *Notch-1*, serving as one of the notch family members (Notch-1, 2, 3, and 4) in Notch pathway and being down-regulated in human airway epithelium in CS and COPD [69], has been found to have a protective role against PKB/Akt activation-mediated anoikis and p53-induced apoptosis in immortalized epithelial cells [70,71], and T-cell receptor-mediated apoptosis in mature cells [72]. Additionally, CSE-induced increase of miR-21 level was observed to increase the excessive autophagic activity as well as promote apoptosis in 16HBECs [26]. The findings suggest CS-induced dysregulation of miR-34a and -21 may promote activation of apoptosis in the development of COPD.

In a CS-related mouse model of COPD and CSE-exposed BEAS-2B, miR-150 was found to be downregulated in airway epithelial cells. Furthermore, its overexpression could inhibit inflammatory response by preventing the induction of IL-6/-8, TNF-α, and NF-κB transcriptional activity in CSE-exposed BEAS-2B cells, as well as protect BEAS-2B cells from CSE-induced apoptosis by directly repressing *p53* expression [27]. Although the exact mechanism for NF-κB inactivation induced by miR-150 is unknown, the inhibition of NF-κB may be derived partly from miR-150-mediated downregulation of *p53* [73]. Those results suggest the anti-inflammatory and anti-apoptotic roles for miR-150 in smoke-related COPD. Interestingly, enrichment of microRNAs including miR-125a, -191 and -126, and let-7d in circulating endothelial microparticles (EMPs) in smokers, may serve as a useful indicator of inflammation concomitantly with apoptosis in CSE [74]. Those observations at least partly indicate that CSE-induced dysregulation of miRNAs leads to the imbalance between apoptosis and replenishment of structural cells in the lung through abnormally modulating their downstream targets, and subsequently contributing to COPD development.

3.1.3. The role of miRNAs in inflammatory response

The inflammation in COPD is characterized by enhanced numbers of alveolar neutrophils, macrophages, and T lymphocytes that are recruited from the circulation and involve the inflammatory response in the airways. Commonly, the inhalation of harmful particles including CS could contribute to the influx of inflammatory cells into the airways and lungs, causing acute or chronic inflammation [3,60]. Although the regulative mechanisms of CS-induced changes of immune cell subsets are little known, however, CSE induced changes of expression of some miRNAs including miR-135b, -152, -30c, -30a-5p, -26a, -218, -21 -142-3p, -146a, -31, and let-7 family members were found to be correlated with dysregulated distribution of various immune cells in the lung and BAL in mice [1,75–77], suggesting that CSE can serve as drivers of miRNA-medicated inflammatory regulation.

Chronic CSE has identified to induce upregulation of miR-101 and -144 in HBECs and the lung of mice, which may suppress *CFTR* that is a chloride channel and involves the pathogenesis of multiple chronic pulmonary diseases including COPD/emphysema [25]. The absence of *CFTR* may promote TNF receptor superfamily member 6 (Fas)-mediated apoptosis by increasing the expression of ceramide and the lipid raft proteins ZO-1 and ZO-2, result in ROS-mediated autophagy inhibition, and induce an NF-kB-mediated inflammatory response in CS-exposed lung cells of mice and human [78,79]. Thus, we can speculate that CS-induced upregulation of miR-101 and -144 can promote apoptosis and inflammatory response in lung cells by inhibiting *CFTR* level, which may contribute to COPD development. Additionally, miR-101 was reported to play a pro-inflammatory role via preventing dephosphorylation of MAPKs by direct inhibition of MKP-1, a dual specific phosphatase that is responsible for the dephosphorylation/deactivation of the MAPK family (ERK, JNK and p38 MAPK) [80–83].

Let-7c expression was demonstrated in bronchial epithelial cells and macrophages that express *TNFR-2*, a known essential player in COPD pathogenesis [84]. CS-induced reduction in let-7c level was found to contribute to COPD/emphysema pathogenesis and decrease the protection against CS-induced inflammation by leading to higher expression of *TNFR-2* in the airways of patients with COPD [18,85]. MiR-34c was found to serve an important role in COPD pathogenesis in which CS-induced reduction of miR-34c increases the expression of its putative target gene, *SERPINE1* that plays a key role in the progression of emphysema/COPD. *SERPINE1* is involved in multiple environmentally pro-inflammatory response induced by activation of inflammatory factors and inflammatory cell migration stimulated by hypoxia, lipopolysaccharide and CS, and oxidative stress [44,86–88]. Furthermore, miR-218, a highly expressed miRNA in the bronchial airway epithelium, is strongly associated with airway obstruction [19]. CSE-induced reduction in miR-218 level was demonstrated to enhance the CSE-induced levels of IL-6/-8, Oligomeric Mucus/Gel-Forming (MUC5AC), and the activation of NF-κB by directly targeting *TNFR1*, which was reversed by increased expression of miR-218 and reduced expression of *TNFR1*. This suggests a mechanism of miR-218 for protection against CS-induced bronchiolitis in COPD, in which miR-218 expression can decrease CSE-induced MUC5AC hyper-production and inflammation via targeting TNFR1-mediated activation of NF-κB [52].

MiR-15b was found to be increased in COPD samples with smoking history and CS-exposed ovarian tissue of mice [43,89]. Its overexpression was showed to directly reduce SMAD7, decorin and *SMURF2* protein expression in Beas2B bronchial epithelial cells. Moreover, miR-15b manipulation could change early *SMAD3* phosphorylation in response to *TGF*-β treatment [43]. Notably, *SMAD7* acts as an inhibitory *SMAD* of the *TGF*-β-induced *SMAD* pathway that is crucial in the modulation of the transcription of genes related to extracellular matrix remodelling and repair, and can be activated by pro-inflammatory cytokines including *TGF*-α and interferon-γ, and has been investigated in the pathogenesis of COPD [43]. Similar to miR-15b, *SMAD7* also influence the phosphorylation of the *SMAD 2–SMAD 3* complex in the *TGF*-β-induced *SMAD* pathway. Interestingly, *SMAD7* exhibited a reduced expression in stage II and stage IV of COPD, but no relationship with smoking status [43]. Those findings suggest that CS-induced miR-15b upregulation directly inhibits *SMAD7* and indirectly decreases the inhibition of SMAD7 to SMAD 2/SMAD 3 phosphorylation, resulting in dysregulation in the transcription of genes related to the pathogenesis of COPD.

Dang et al. [90] found that miR-24-3p, -93-5p, -320a/b, and -1273 g-3p mainly target some pro-inflammatory genes in two the most enriched pathways including NOD-like receptors (*NLRs*) and Toll-like receptors (*TLRs*). *TLRs* are usually present in sentinel cells including macrophages and dendritic cells, involve the first line of defense against invading pathogens as well as play important roles in inflammation, immune cell regulation, survival, and proliferation. *NLRs* are found in dendritic cells, macrophages, lymphocytes and also in nonimmune cells such as epithelium. They play critical roles in regulation of host immune response [91,92]. Additionally, *NLRs* can cooperate with *TLRs* and modulate inflammatory and apoptotic response [92]. As downstream factors of the two pathways, pro-inflammatory modulators including *TNF*, *IL-18*, *IL-1*β, *CCL3* and *CCL4* were observed to be downregulated in PBMCs of COPD patients. In *NLR* pathway, miR-24-3p was predicted to modulate *IL18/IL1B/TNF*, as well as miR-93-5p to modulate *NLRP3/IL6/NFKBIA*. In *TLR* pathway, miR-24-3p was predicted to modulate *CCL3/CCL4/IL1B/TNF*, as well as miR-93-5p to modulate *IL6/CXCL10/NFKBIA* [90]. CS-induced miR-149-3p downregulation in murine monocytic cell line THP-1 may enhance the inflammatory response in COPD patients by modulating the *TLR-4/NF-κB* signaling pathway in which downregulation of miR-149-3p promotes the *TLR-4/NF-κB* signaling pathways and increases the secretion of pro-inflammatory cytokines such as *IL-1*β and *TNF*-α [20].

In addition, CS-induced miR-195 upregulation was observed to elevate Akt phosphorylation and increase *IL-6* and *TNF*-α levels in BEAS-2B cells via directly inhibiting expression of *PHLPP2*, a member of the Ser/Thr protein phosphatase family, and this contributes to CS-induced COPD pathogenesis. However, knockdown of miR-195 suppressed CS-induced lung pathological changes, and decreased

inflammatory cell infiltration, as well as production of tumor necrosis factor-α and interleukin-6 in BLA [15]. Akt was widely reported to serve as a potential modulator in COPD, which can be phosphorylated via CS, cytokines, and growth factors [93]. Its inhibition was indicated to defense against Nrf2-regulated cellular oxidative toxicity by directly promoting Akt phosphorylation [59,94]. Nevertheless, the contradictory that inhibition of *PHLPP2* may both augment the inflammatory response and promote defenses against oxidative injury needs to be explored. Functional assays demonstrated that via inhibiting expression of *CCN1* that is a member of CCN protein family, and as a central signal dispatcher modulating the direction of lung pathogenesis including apoptosis, inflammation, and fibrosis, overexpression of miR-181c can reduce the inflammatory cytokines including IL-6 and IL-8 and inflammatory response, ROS generation, and neutrophil infiltration induced by CS, whereas its downregulation emerged the opposite effects [21,95], indicating that miR-181c is a protector for lung injury in COPD.

The distinct CSE duration can cause different changes of miRNAs and immune cell subsets [1]. In the following forced smoking for varying time periods, the lung pathogenic process of COPD such as the numbers of inflammatory infiltrates in the lungs and the global expression profiles of miRNA expression in the lungs with different stages of COPD were dynamically changed [96]. CS may modulates miRNA expression and gene expression correlated with the pathogenesis of smoking-induced pulmonary disease, as well as some of these alterations persist although smoking cessation [97–99], which may partly explain the sustained higher risk of the development of COPD and lung cancer in healthy smokers compared to healthy nonsmokers [100]. Thus, to reverse persistent changes of dysregulated miRNAs after smoking cessation may be a possible strategy.

3.2. The role of miRNAs in the air pollutant-induced regulation of pathways involved in the mechanisms of COPD

Early air pollution exposure including indoor and outdoor particulate matter (PM), nitrogen dioxide (NO2) and ozone (O3), etc. during in utero and postnatal life could result in pulmonary and other disease development in later life [101,102]. The pathologic effects of air pollution in the lung are similar to CS, with them being mediated by inflammatory pathways as well as involving oxidative stress [34]. Epidemiological studies showed the adverse effect of air pollution on modifications in gene expression profiles, which may be involved in modulation from miRNAs. It has showed that particulate air pollution exposure in early life could alter the expression of miRNA-222, -21, and -146a, as well as miR-2's downstream target gene, phosphatase and tensin homolog (*PTEN*) in human placental tissue. *PTEN*, a predisposing gene of COPD, is a critical modulator of cell cycle progression and cellular survival by the AKT signaling pathway. Those suggest that in utero air exposure can change the expression of miRNAs that be relevant targets for particulate air induced effects in fetal programming, potentially causing adverse health outcomes later in life [35,36]. Alteration of miR-222 related with oxidative stress and inflammatory processes was identified not only in blood leukocyte of adult but also in the extracellular fraction of saliva of primary school children under PM exposure [38,39], suggesting the similar inflammatory responses of miR-222 mediating to PM in different life stages.

Krauskopf et al. performed next-generation sequencing and bioinformatics analysis and identified 54 circulating miRNAs (cmiRNAs) to be dose- and pollutant species-dependently related to PM2.5, PM10, NO2, black carbon, and ultrafine particles already after 2 h of exposure with an equal expression level of the most abundant cmiRNAs between plasma and all organs including the lung, heart, kidney and brain known to be targeted by these traffic-related air pollution [101]. This indicates potential of cmiRNAs as novel biomarkers for air pollution exposure. Motta et al. demonstrated that acute PM exposure can directly or indirectly regulate inflammatory gene expression via PM-responsive miRNAs. In this report, four differentially upregulated miRNAs including miR-146a, miR-421, miR-29a, and let-7 g in blood samples were showed to play roles in inflammation or responses to environmental toxicants [37]. Of which miR-29a may directly suppress the expression of *PTEN* by binding the 3′UTR of *PTEN* mRNA [103], which promotes a proinflammatory response [104]. Furthermore, miR-146a can directly inhibit the expression of signal transducer and activator of transcription 1 (*STAT1*) that is a transcription factor that elevates *CCL2* proinflammatory gene transcription [37]. Another study also found that workers exposed to metal-rich PM have dysregulated expression of miRNAs including miR-21, -222, and -146a, which may contribute to inflammation and oxidative stress induced by PM [38]. Although the exact roles of miRNAs in the cellular response to air toxicants are little known, those results suggest that PM-induced systemic inflammation is partly mediated by miRNA, and show that miRNAs are environmentally sensitive inhibitors of some gene expression regulating the effects of air pollution toxicants on human body.

In view of the number limitations of air pollution exposure-miRNA-COPD study, the mechanisms of environmental effects on differential miRNA expression in COPD patients are little known. Even so, Ebrahimi et al. [40] reviewed different expression profiles of miRNAs in air pollutants. Twenty four miRNAs were downregulated and 5 were upregulated in smoke exposed human epithelium cell, whereas 67 miRNAs in human epithelial cells exposed to diesel exhaust particle were downregulated and 130 upregulated. Air pollution was reported to promote the symptoms of COPD and cause alterations in miRNA expression in patients with COPD in the Beijing group, the migratory group as well as the healthy control group. In this report, the differentially inhibited regulation of those miRNAs on major pro-inflammatory cytokines include *TNF* and *IL-1*, and anti-inflammatory cytokines include *IL-1* receptor antagonist, *IL-4*, *IL-6*, *IL-10*, *IL-11* and *IL-13* in three groups was found [55].

3.3. The roles of miRNAs in infection-induced exacerbations of COPD

Acute exacerbation of COPD (AECOPD) can cause a reduced quality of life of patients and lung function and an elevated risk of death [105,106]. Patients with COPD have elevated predisposition to influenza A virus (IAV) infections which cause acute exacerbations and adverse outcome [107], and respond poorly to vaccination due to strong drug resistance of IAVs [108]. IAV infection induces increased inflammatory and impairs antiviral responses in subjects with COPD [109–111]. Presently, miR-125a/b was demonstrated to directly decrease the expression of *A20* as well as mitochondrial antiviral signaling (*MAVS*), and lead to exaggerated inflammation and impaired antiviral responses under IAV infections in in vivo and in vitro of COPD [23]. Additionally, miR-203 was reported to be significantly upregulated in lung tissues and blood both from non-COPD smokers and COPD patients compared with non-smoke controls, and demonstrated to function as an immune response inhibitor of *NF-κB* signaling activation via targeting and suppressing *PIK3CA* and *TAK1* and contribute to the predisposition to bacterial infection and the COPD initiation [16]. Those findings indicating a potential of those reported miRNAs as antiviral therapy target in respiratory diseases with virus infections.

3.4. The correlations of miRNAs with abnormal lung function

CSE may lead to aberrant FEV1/FVC% and/or FEV1% in COPD patients and abnormal FEV1% in healthy population, however, the exact mechanism is little known. Ten miRNAs including miR-34b/c, -133a/b, -149, -125a-5p, -451a, -106b-5p, -29c, and -126 were reported to be differentially expressed in distinct degrees of COPD patients [17,23,44]. Furthermore, the expression of at least 10 mRNAs including miR-1273 g-3p, -126, -503, -34b/c, -342-3p, -30e-3p, -125a-5p, and let-7c was observed to be positively associated with FEV1% [18,28,90,112]. However, the levels of miR-106b-5p, -15b, -195, -24-

3p, -320a, -320b, -34a, and -199a-5p were suggested to inversely correlate with FEV1% [15,23,24,43,90]. Additionally, miR-125b, -218, and let-7c were indicated to positively correlate with FEV1/FVC% [18,52]. MiR-503 was showed to have a positively association with FVC% in COPD [28]. Those results suggest that miRNA evaluations may give information about the staging and prognosis of COPD.

The diagnosis of COPD is based on abnormal function as measured by spirometry. However, not all patients can have lung function tests because of contraindications for lung function test. Thus, the detection of biomarkers for COPD severity such as analysis of lung function-related miRNAs may be a promising strategy for evaluation of this disease.

4. The role of miRNAs in genetic predisposition of COPD

The growing studies demonstrated that variants in miRNA genes contribute to COPD development. MiRNAs modulate gene expression via binding to partly complementary sequences within target mRNA transcripts, thus resulting in their degradation, deadenylation, or suppressing their translation [113]. For example, miRNAs modulate the transcriptional activity of multiple genes associated with inflammation and lung function that involve the pathogenesis of COPD [114]. However, variants in miRNA genes may alter miRNA regulation to target mRNA, leading to multiple human disease occurrence including COPD [48,115,116]. Thus, partial predisposition of COPD may result from epigenetic regulation of miRNAs.

MiR-196a2 locates within the region of homeobox (*HOX*) gene clusters on chromosome 12q13.13. Network analysis and experimental studies demonstrated that miR-196a2 targets some key genes in COPD pathogenesis including *GSTP1*, *ACE*, *HTR4*, *PPT2*, and *THSD4* that involve immune cell trafficking and inflammation, as well as cell-to-cell signaling, and targets platelet-derived growth factor receptor alpha polypeptide (*PDGFRA*), collagen type 3 alpha 1 (*COL3A1*), collagen type 1 alpha 1/2 (*COL1A1/COL1A2*), erythrocyte membrane protein band 4.1-like 2 (*EPB41L2*), and calcium/calmodulin-dependent serine protein kinase (*CASK*) genes involved in cell junction and communication. Additionally, miR-196a2 is associated with genes involved in apoptosis by mTOR signaling pathway and proteolysis including matrix metalloproteinases 23 B (*MMP23B*), Rapamycin-insensitive companion of mTOR (*RICTOR*), and mitogen-activated protein kinase (*MAPK*). Those two pathways are closely related to emphysematous parenchymal destruction and extracellular matrix degradation in COPD [9]. The T allele and the TT genotype of miR-196a2 rs11614913 were showed to significantly associate with a reduced risk for COPD, compared to the C allele and the CC genotype [113], while CC genotype of rs11614913 was found to increase the risk of non-small cell lung cancer that is one of the most common comorbidities in patients with COPD [48]. In addition, COPD patients with CC showed the smallest bronchodilator response after Salbutamol inhalation, the CT genotype had an intermediate response, whereas those with TT showed the highest response. This may be partly explained by that miR-196a2 targets molecules essential for the regulation of both actin cytoskeleton pathways and calcium signaling, which in turn medicates downstream effectors essential for actinomyosin assembly contraction, actin polymerization, long-term potential, and phosphatidylinositol signaling pathway [9]. Taken together, although the exact regulation of miR-196a2 in genes involved in COPD pathogenesis is little known, it can be deduced that rs11614913 single nucleotide polymorphisms (SNP) of miR-196a2 play an important role in COPD susceptibility.

MiR-146a-5p, demonstrated as a modulator of cellular function in both innate and adaptive immunity [117], has been showed to target multiple inflammatory pathways including IL-1 receptor and Toll-like receptor signaling [118]. In a study by Osei et al. miR-146a-5p was demonstrated to negatively modulate *IL-1* signaling. By downregulation of *IL-1* receptor-associated kinase-1, miR-146a-5p overexpression may reduce *IL-1*α-induced *IL-8* secretion in primary human lung fibroblasts (PHLFs) derived from COPD patients, suggesting an anti-inflammatory effects of miR-146a-5p on lung fibroblasts [119]. Similar to this finding, in another report by Jiang et al., miR-146a-5p overexpression was showed to directly reduce TNF receptor-associated factor (*TRAF*)-*6* and *IL-1* receptor-associated kinase (*IRAK*)-*1* expression, which are downstream of the *IL-1* pathway, as well as attenuate the release of pro-inflammatory cytokines via inhibiting *NF-κB P65* in hypoxia/reoxygenation (H/R)-induced macrophages [117,120]. In addition, miR-146a was showed to be downregulated by activated NF-kB pathway in smokers with COPD [29], leading to an enhanced production of prostaglandin E2 (*PGE2*) and elevated expression of cyclooxygenase-2 (*COX-2*) in the fibroblast cells derived from smokers with COPD [46]. *COX-2* and its product *PGE2* were demonstrated to have crucial roles in airway inflammation, and in contribution to the severity of airflow limitation regulated via MMP-2 in COPD progression [121]. *PGE2*, which is involved in controlling lymphocyte trafficking as well as differentiation in multiple models [122,123], was reported to suppress LPS-induced *NF-κB* activation in monocytes, thus inhibiting *TNF*-α expression whereas enhancing the anti-inflammatory cytokine, interleukin (IL)-10 [124–126]. Taken together, those findings indicate a key role of miR-146a in inhibiting smoke-induced damage within the lung via acting as an “inflammatory brake”. In addition, the CC/GC genotype of miR-146a rs2910164 was showed to more common in COPD than GG genotype [116]. The C allele of rs2910164 was demonstrated to contribute to a decrease of mature miR-146a [127]. Similarly, rs2910164 CC/GC was found to elevate the expression level of *COX2* and its catalytic product *PGE2* by decreasing miR-146a [116]. Furthermore, miR-146a was thought to serve as a tuning mechanism to protect an overstimulated inflammatory state via a negative feedback regulatory loop relating to inhibition of *IRAK1* and *TRAF6* [117,128,129]. This also partly explains why smokers present the downregulation of miR-146a by activated NF-kappaB pathway. Those results indicate that rs2910164 CC/GC may reduce COPD risk by enhancing “inflammatory brake” effect of miR-146a-5p.

5. Conclusion

COPD is a multifactorial disease caused by environmental and genetic risk factors. However, few studies have successfully uncovered the pathogenetic mechanisms and predisposition for COPD. The rate of diagnosised COPD is very high and the elevated risk of underdiagnosis is one further central feature of COPD epidemiology [130]. For mild to moderate disease processes, more than 60% of patients are estimated to are undiagnosed [131]. As the progressive nature of the disease and heterogeneity of pathogenic factors, FEV1 typically reduces over time, and variable clinical manifestations, low survival quality and life, and comorbidities of COPD are significantly increased in patients [132,133]. Therefore, to reveal the pathogenesis of COPD and find accurate diagnostic methods and protective strategies of this disease is pivotal and urgent at present and in the future.

As shown in Fig. 1, a great deal of in vitro and in vivo studies have suggested that environmental exposure such as CS and air pollutants can dysregulate miRNA expression profiles in distinct samples from patients with/without COPD, subsequently disturbing the regulative effects of them on COPD-related genes in the key signaling pathways involved in the mechanisms of COPD, including influx of inflammatory cells into the lung, oxidative stress, and the imbalance between apoptosis and replenishment of structural cells in the lung (Fig. 2). The distinct exposure time of the similarly environmental risk factors and distinct environmental factors lead to different degree of clinical manifestation such as inflammatory response, and different miRNA expression profiles. Although environmental exposure cessation, those irreversible harmful changes including aberrant miRNA expression and chronic inflammation in the lung are still persistent.

Those functionally COPD-related genes that are almost involved in the all autosomes and modulated by miRNAs have been summarized

(Table 1 and Table 2). Under the exposure of environmental factors, those genes play important roles in the pathogenesis of COPD. However, even though under the same environmental exposure status, the different population would have distinct response. For example, there are many differential expressed miRNAs and clinical manifestation between smokers with COPD and smokers without airway limitation. Those suggest that susceptible individuals of COPD have specific response upon distinct toxicants. However, some functional miRNAs at least partly contribute to specific response procession. SNPs of miRNA genes have been demonstrated to involve the predisposition of COPD. As summarized in Fig. 3, the functional SNP variant (for example C converts to G) within some miRNAs might influence miRNA by affecting processing of the pre-miRNA to its mature form, and influence the regulative effects of miRNAs on mRNAs involved in mechanisms of COPD, which may lead to COPD susceptibility of individuals with those variants.

Taken together, environmental exposure can cause dysregulated miRNA expression profiles, leading to biological response such as oxidative stress, inflammation, and apoptosis in various samples of human. Unfortunately, those cumulative biological effects contribute to the pathogenesis of COPD in susceptible individuals. In view of the evidence, avoiding environmental exposure such as smoking cessation is an appropriate strategy to reduce COPD risk. Prevention of respiratory infection may induce acute exacerbations and adverse outcome for patients with COPD. Additionally, some important miRNAs such as miR-218, -203, -146a, as well as miR-34 family (-34a/b/c) and let-7 family have the potential of serving as potential fluid biopsy-based markers for environmental risk and COPD risk. Notably, functional circulating miRNAs that regulate COPD-related genes involved in key signaling pathways associated with the mechanisms of COPD are expected to act as drug targets. However, the diversity of miRNA expression profiles among different COPD population needs to be explored in the future studies. In addition, it is necessary to research the exact roles of miRNAs in differently predisposed population exposed to different environmental factors.

Abbreviations[2]

COPD	Chronic obstructive pulmonary disease
MiRNAs	microRNAs
SNPs	single nucleotide polymorphisms
CS	Cigarette smoke
CSE	Cigarette smoke exposure

Summary conflict of interest statements

No conflicts of interest, financial or otherwise, are declared by the authors.

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