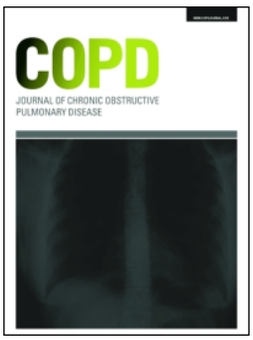

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REVIEW

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Epigenetic Modifications and Therapy in Chronic Obstructive Pulmonary Disease (COPD): An Update Review

Lingzhi Zhang[a]*, Hamed Valizadeh[b,c]*, Iraj Alipourfard[d,e], Ramtin Bidares[f], Leili Aghebati-Maleki[g], and Majid Ahmadi[h,i]

[a]Department of Emergency Medicine, Shengjing Hospital of China Medical University, Shenyang, China; [b]Department of Internal Medicine and Pulmonology, Faculty of Medicine, Urmia University of Medical Sciences, Urmia, Iran; [c]Tuberculosis and Lung Disease Research Center, Tabriz University of Medical Sciences, Tabriz, Iran; [d]Faculty of Life Sciences, Center of pharmaceutical sciences, University of Vienna, Vienna, Austria; [e]Faculty of Sciences, School of Pharmacy, University of Rome Tor Vergata, Roma, Italy; [f]Department of Experimental Medicine, Sapienza University, Rome, Italy; [g]Immunology Research Center, Tabriz University of Medical Sciences, Tabriz, Iran; [h]Stem Cell Research Center, Tabriz University of Medical Sciences, Tabriz, Iran; [i]Student Research Committee, Tabriz University of Medical Sciences, Tabriz, Iran

ABSTRACT

Chronic obstructive pulmonary disease (COPD) that is one of the most prevalent chronic adult diseases and the third leading cause of fatality until 2020. Elastase/anti-elastase hypothesis, chronic inflammation, apoptosis, oxidant-antioxidant balance and infective repair cause pathogenesis of COPD are among the factors at play. Epigenetic changes are post-translational modifications in histone proteins and DNA such as methylation and acetylation as well as dysregulation of miRNAs expression. In this update review, we have examined recent studies on the upregulation or down-regulation of methylation in different genes associated with COPD. Dysregulation of HDAC activity which is caused by some factors and miRNAs plays a key role in the suppression and reduction of COPD development. Also, some therapeutic approaches are proposed against COPD by targeting HDAC2 and miRNAs, which have therapeutic effects.

Abbreviations: COPD: Chronic obstructive pulmonary disease; NF-κB: Nuclear factor kappa-B; DNMT: DNA methyl transferase; mtTFA: Mitochondrial transcription factor A; GST: Glutathione S-transferase; HTR4: 5-hydroxytryptamine Receptor 4; BID: BH3 Interacting Domain Death Agonist; PRMTs: Protein arginine methyl transferases; CARM1: Coactivator-associated arginine methyl transferase 1; HDACs: Histone/protein deacetylases; JNK: C-Jan N-terminal kinases; TSLP: Thymic stromal lymphopoietin; MCP-1: Monocyte chemoattractant protein-1; IGF: Insulin-like growth factor; TLR: Toll-like receptor; IL-1: Interleukin-1; TNF: Tumor Necrosis Factor; PPARγ: Peroxisome proliferator-activated receptor gamma

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Introduction

Mucociliary dysfunction, lung inflammation, airway fibrosis and alveolar destruction characterize chronic obstructive pulmonary disease (COPD), which is a widespread chronic adult disease and the third leading cause of fatality worldwide by 2020 [1]. There are several factors at play such as chronic inflammation, elastase/anti-elastase hypothesis, apoptosis, oxidant-antioxidant balance and infective repair cause pathogenesis of COPD [2,3]. Containing more than 4700 chemical compounds and 1014 free radicals/oxidants, cigarette smoke is the major cause of the pathogenesis of COPD and inflammation [4]. It activates different redox sensitive transcription factors such as nuclear factor kappa-B (NF-κB), resulting in elevated expression of pro-inflammatory cytokines and chemokines in COPD [5,6]. Epigenetic alterations are post-translational modifications in histone and other DNA proteins [7]. DNA methylation and histone methylation can affect gene expression without changing the primary gene sequence. Some post-translation modification on histone proteins (H2A, H2B, H3 and H4) contains acetylation, phosphorylation and ubiquitination [8,9]. DNA methylation is the primary mechanism in epigenetic catalyzed by DNA methyl transferase (DNMT) family members where methyl groups are added the cytosine residues in Cytosine phosphate—Guanine (CpG) islands [10,11]. Hypermethylation of DNA in gene promoter regions of CpG islands usually causes gene silencing and hypomethylation which triggers transcription activation of DNA [10]. Histone are important protein components of chromatin. Chromatin consists of linker H, and protein octamer including two copies of each core histone H2A, H2B, H3 and H4 where DNA is wrapped [12,13]. Histone modification play an essential role in gene regulation by H3K4me3, H3K9me3 and H3K27me3. H3K4me3 is correlated with the activation of gene expression, but H3K27me3 and H3K9me3 are associated with gene expression [12].

CONTACT Lingzhi Zhang datar7@126.com Department of Emergency Medicine, Shengjing Hospital of China Medical University, Shenyang 110004, China; Majid Ahmadi Ahmadi.m@tbzmed.ac.ir Stem Cell Research Center, Tabriz University of Medical Sciences, Golgasht Street, Tabriz 5166/15731, Iran
*Lingzhi Zhang and Hamed Valizadeh contributed equally to this manuscript.

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Non-coding RNAs or microRNAs (miRNAs) are other post-transcriptional regulators of genes expression through mRNA degradation and disruption [14]. miRNAs are 21–23 nucleotides and RNA polymerases can generate miRNAs *via* transcription of primary RNA. Studies have shown more than 60% of the protein-coding genes regulated by miRNAs, which is performed by binding miRNAs to the 3/-untranslated region (3/-UTR) or binding the 5/UTR region of mRNA to elevate cleavage or suppress translation [15,16].

Epigenetic and COPD

Epigenetic changes are heritable changes in genes expression *via* histone or DNA sequence modification [7,17]. It has been demonstrated that epigenetic changes including miRNAs dysregulation, histone acetylation and deacetylation and aberrant DNA methylation, inflammatory genes actives abnormal in COPD [18]. Epigenetic phenomena can affect response to cigarette smoke and oxidants in lung epithelial cells and macrophages in COPD patients and the lung of smokers [19]. Acetylation and deacetylation of histones, upregulation and downregulation of DNA methylation and miRNAs activity can cause chronic lung diseases such as asthma and COPD [20]. Cigarette smoke extract (CSE) increased epigenetic changes such as those in mitochondrial DNA (mtDNA) and subsequently higher COPD [21]. Studies have shown that air pollution has various methylated signals at C-phosphate-G (CpG) regions of COPD patients [22].

DNA methylation and COPD

Expression of pro-inflammatory genes is regulated by DNA methylation and subsequently suppresses the development of COPD. In both alveolar macrophages and epithelial cells of COPD patients, DNA methylation of the promoters of pro-inflammatory genes has been found [23]. DNA methylation is found to have a critical role in the presence and development of COPD; also, DNA methylation can be altered by cigarette smoking through stimulating inflammatory response and causing diseases such as COPD [24]. Macrophages are members of innate immune cells with lung macrophages having an important effect in the polarization of innate and adaptive immunity as well as recognition and elimination of bacteria [25]. COPD usually occurs with upper lobe predominance, and studies have demonstrated physiology variation in ventilation and oxygenation between the upper and lower lobes of lung [26]. Armstrong *et al.* [27] have reported that several genes of lung macrophages including HSH2D (Hematopoietic SH2 Domain Containing), SNX10 (Sorting Nexin 10), CLIP4 (CAP-Gly domain Containing linker protein family member 4) and TYKZ are 95 CpG loci with significant difference of methylation. Mitochondrial transcription factor A (mtTFA) has a central role in mitochondrial operations and pathophysiology conditions such as necrosis, immune responses and inflammation [28]. The expression of mtTFA was remarkably decreased in the skeletal muscle of COPD patients [29]. mtTFA regulates both mitochondrial DNA (mtDNA) copy number and mitochondrial transcription initiation by binding the upstream of the heavy strand promoter1 (HSP1) and light strand promoter (LSP) of mtDNA [30]. Peng *et al.* [21] have demonstrated that cigarette smoke elevated hypermethylation of the mtTFA promoter and triggered COPD. Air pollution is correlated with different illnesses such as COPD [31]. Epigenetic changes including altered DNA methylation can happen by air pollution promoters [32]. Some ambient air pollution such as those with particle matter <10 um in diameter (PM10) are associated with 12 differentially methylated probes (DMPs) and 27 differentially methylated regions (DMRs) in CpGs in NEGR1 (Neuronal growth regulator 1), ARID5A (AT-Rich Interaction Domain 5 A), FOXl2 (Forkhead Box 12), WDR46 (WD Repeat Domain 46), AKNA (AT-Hook Transcription Factor) and SYTL2 (Synaptotagmin like 2) genes. Also, nitrogen dioxide (NO2) correlated with 45 DMPs and 57 DMRs in CpG in some genes including ERI3 (ERI1 Exoribonuclease Family Member 3), RPL5 (Ribosomal Protein L5), CPLX1 (Complexin 1) and STON1 (Stonin 1) [22]. Fibroblast are found in the airways, adventitia of the vasculature, stroma of many tissues and parenchyma of adult lungs [33]. Lung fibroblasts are essential for homeostasis of the extracellular matrix (ECM) lung repair and stem cells maintenance [34,35]. In COPD patients, airway and parenchymal fibroblasts differ in response to TGFβ, proliferation rate and physiological extracellular matrix (ECM) [36]. Differentially methylated regions were detected in airway fibroblast in COPD, six hundred and fifty two of which were located in known genes such as TMEM44 (Transmembrane Protein 44), RPH3AL (Rabphilin 3 A like), WNT3A (Wnt family member 3 A), HLA-DP1 (Major Histocompatibility Complex, class II, DP beta 1) and HLA-DRB5 (Major Histocompatibility Complex, class II, DR beta 5) [33]. On the other hand, Clifford *et al.* [33] demonstrated 44 DNA differentially methylated regions including at least three CpG sites in HLX (H2.0 like Homeobox) genes which are hypermethylated in COPD but hypomethylated in NXN (Nucleoredoxin) gene. SERPINA1 (Serpin Family A member 1) gene expression variants might increase COPD risk and associated lung function phenotypes. Methylation of SERPINA1 at two CpG in smoking adults associated with COPD [37]. Excessive mucus secretion and production and goblet cell metaplasia can cause COPD [37]. The tracheo bronchial epithelium of the human airways include club (clara) cell, basal cells, neuroendocrine cells and ciliated cells [38]. Forkhead box protein A2 (foxA2) and Transcription factors SAM-pointed domain containing ETS-like factor (SPDEF) genes are two crucial regulators for goblet cell differentiation. FoxA2 is an inhibitor of goblet cell differentiation in lung whereas SPDEF is critical for mucus production and goblet cell differentiation [39,40]. Song *et al.* [41] have found that hypomethylation of CpG numbers are 11 in the foxA2 promoter and hypomethylation of CpG numbers are 6 in the SPDEF (SAM Pointed Domain Containing ETS Transcription Factor) promoter. Sphingosine-1 phosphate (S1P) is necessary for macrophage function *via* phagocytosis and promoting maturation [42]. Studies have examined that

Table 1. DNA methylation changes in COPD.

Epigenetic changes	Target gene	Mechanism	References
Dysregulation of methylation	HSH2D, SNX10CLIP4, TYKZ	variation of ventilation and oxygenation between the upper and lower lobes of lung	[28]
Hyper methylation	mtTFA	Dysregulation of mitochondrial transcription initiation by light strand promoter (LSP) of mtDNA	[21]
Dysregulation of methylation	NEGR1, ARID5A, FOXI2, WDR46, AKNAERI3, RPL5, CPLX1	Affect by pollution promoterssuch as (PM10) and (NO2)	[22]
Dysregulation of methylation	TMEM44, RPH3AL, WNT3A, HLA-DP1 HLA-DRB5	airway and parenchymal fibroblasts differ in response to TGFB and physiological extracellular matrix (ECM)	[36]
Hyper methylation	SERPINA1	Excessive mucus secretion and production and goblet cell metaplasia	[37]
Hyper methylation	foxA2	Dysregulation of goblet cell differentiation in lung	[41]
Hyper methylation	S1P	Dysregulation of macrophage function	[43]
Hyper methylation	NOS1AP, TNFAIP2, GABRB1 BID	Effect by Cigarette smoking	[45]
Hypo methylation	AHRR SERPINA1	Effect by Cigarette smoking	[48]
Hypo methylation	IGF1R –	Suppress Lung development	[46]

HSH2D (Hematopoietic SH2 Domain Containing), SNX10 (Sorting Nexin 10), CLIP4 (CAP-Gly domain Containing linker protein family member 4), Mitochondrial transcription factor A (mtTFA), NEGR1 (Neuronal growth regulator 1), ARID5A (AT-Rich Interaction Domain 5 A), FOXI2 (Forkhead Box 12), WDR46 (WD Repeat Domain 46), AKNA (AT-Hook Transcription Factor) and SYTL2 (Synaptotagmin like 2), TMEM44 (Transmembrane Protein 44), RPH3AL (Rabphilin 3 A like), WNT3A (Wnt family member 3 A), HLA-DP1 (Major Histocompatibility Complex, class II, DP beta 1) and HLA-DRB5 (Major Histocompatibility Complex, class II, DR beta 5), SERPINA1 (Serpin Family A member 1), Forkhead box protein A2 (foxA2), Sphingosine-1 phosphate (S1P), NOS1AP (Nitric Oxide Synthase 1 Adaptor Protein), TNFAIP2 (TNF Alpha Induced Protein 2), GABRB1 (Gamma-Aminobutyric Acid Type A Receptor Beta 1 subunit), BID (BH3 Interacting Domain Death Agonist), AHRR (Aryl-Hydrocarbon Receptor Repressor).
Coactivator-associated arginine methyl transferase 1 (CARM1), nuclear factor κB (NFκB), histone/protein deacetylases (HDACs).

dysregulation of S1P gene expression is correlated with alveolar macrophages in COPD [43]. In smokers, the methylation of S1P is reduced compared with non/ex-smokers [44]. Sunder *et al.* [45] have shown that DNA methylation of NOS1AP (Nitric Oxide Synthase 1 Adaptor Protein), TNFAIP2 (TNF Alpha Induced Protein 2), GABRB1 (Gamma-Aminobutyric Acid Type A Receptor Beta 1 subunit) and BID (BH3 Interacting Domain Death Agonist) are hypermethylated in both COPD and smoker compared to health group. AHRR (Aryl-Hydrocarbon Receptor Repressor) and SERPINA1 genes were significantly hypomethylated in COPD and the smoker group. In lung development, the Insulin-like growth factor (IGF) system has a central role especially IGF1 and IGF1R [46,47]. KF *et al.* [48] proved that smoke induces a CpG site specific loss of IGF1R promoter methylation. Recent studies have generally the ability of smoke to affect and change DNA methylation and subsequently COPD. In a study conducted in 2014, it was proven that 97% of the DNA methylation probes were hyper methylated in COPD small airway group compared to normal small airway group, which are located various genes such as three cholinergic receptors (CHRND, CHRNB1, CHRNB2), GPR126 (G protein-coupled receptor 126), HTR4 (5-hydroxytryptamine Receptor 4), EPHX1 (Epoxide hydrolase 1) as well as three glutathione S-transferase (GST) genes (GSTT1, GSTM1 and GSTP1). On the other hand, some DNA methylation probes were hypomethylated in KSR1 in COPD group and these variation of DNA methylation are positively correlated with smoking. DNA methylation of genes related to COPD are summarized in Table 1. [49].

Histone modification by dysregulation of HDAC2 and COPD

Histone deacetylation and histone acetylation comprise two enzyme families and play an effective role in the occurrence of inflammation in COPD [50]. On specific lysine residues, histones H3 and H4 are acetylated. Studies proved the changeability of the acetylation/deacetylation balance toward acetylation in patients with COPD and resultant inflammation [51]. Acetylation of H3 can be induced by cigarette smoke in the lung of humans and macrophages [18]. Histone deacetylases (HDACs) regulate protein operation and gene transcription through regulating the histone acetylation levels. Many large macromolecular complex and transcription factors are regulated by HDACs in cellular processes [52]. Previous studies have demonstrated the suppression of HDAC1 and HDAC2 in skeletal muscle during the perinatal period, leading to the death of a proportion of mice pups due to sarcomere degeneration and mitochondrial abnormalities [53]. HDAC1/2 was elevated in the mice treated with cigarette smoke (CS) [54]. Thus, HDAC1/2 may have a role in skeletal muscle atrophy. Ding *et al.* [54] reported Trichostaina (TSA) which is a HDAC inhibitor can be a therapeutic approaches by inhibition of HDAC1/2, which finally suppresses skeletal muscle atrophy and histomorphological alteration in COPD patients. The second important histone modification is the addition of methyl group to arginine residues by protein arginine methyl transferases (PRMTs) in both histone and non-histone proteins [55]. Coactivator-associated arginine methyl transferase 1 (CARM1) have an impact in transcriptional regulation *via* demethylase arginine residues of histone H3 and different non-histone proteins [56,57]. CARM1 expression is downregulated during epithelial cells injury in COPD but it is upregulated in normal epithelial cells [58]. Therefore, CARM1 is crucial for the regeneration and repair of airway epithelial cells *via* regulating cellular senescence. Particulate matter (PM) such as fine (FP) and quasi-ultrafine (UFP) can reduce HDAC activity lifting HAT/HDAC ratio. H3K9 histone acetylation was high in COPD-diseased human bronchial

epithelial (DHBE) group and in the group mentioned above[59]. Cigarette smoking and oxidative stress are two major features to inhibit inflammation in lung parenchyma and airways in COPD [60,61]. Oxidative stress can activate the nuclear factor κB (NFκB) causing higher proinflammatory cytokines and subsequent COPD [62]. Sirtuins are members of the silent inflammation regulator 2 family that they belong to class III histone/protein deacetylases (HDACs) [63]. Silent inflammation regulator 1 (SIRT1) is associated with inflammation, cell aging, senescence and COPD/emphysema [64]. Studies have shown that SIRT1 regulates NFκB and decreased inflammatory responses [65]. Ma *et al.* [66] found that erythromycin elevated SIRT1 expression and subsequently suppressed NFκB acetylation and pro inflammatory cytokines in COPD. FoxO3 belongs to the Fox family and is demonstrated in COPD patients where the interaction between the SIRT1 and foxO can inhibit NFκB activity [67]. Vincenzo *et al.* [68] proved that CSE dysregulates the NFκB activity and elevates inflammatory responses *via* impairing the function of SIRT1/FoxO3 [68]. Reducing HDAC2 is crucial for glucocorticoid-dependent anti-inflammatory activity, but the oxidant stress and inflammation rise by reduced HDAC2 [69,70]. Cigarette smoking elevated oxidant stress and promoted COPD glucocorticoid resistance which was associated with higher HDAC2 activity [71]. As a peptide, LL-37 has the ability of suppressing the AKt signal pathway and C-Jan N-terminal kinases (JNK) and inhibiting the proinflammatory cytokine activity [72]. Zhen *et al.* [73] demonstrated LL-37 enhanced activity and expression of HDAC2 *via* the inhibition of PI3K (Phosphatidylinositol 3-kinase)/AKt pathway in COPD patients. Theophylline is the inhibitor of phosphodiesterase isoenzymes that prevents NFκB activation and its translocation into the nucleus and suppresses inflammatory genes in COPD [74]. Cigarette smoke extract (CSE) can enhance NFκBp65 protein and activity as well as TNF-α and IL-8 levels in murine skeletal muscle cells in COPD [75]. Through upregulating HDAC2 expression and downregulating NFκBp65 (Nuclear Factor Kappa B) activity, Theophylline has an anti-inflammatory effect in COPD patients [76]. NFkB is activated by phosphorylation and degradation of inhibitor kappa B (IκB) and results in transcription of NFκB dependent gene [77]. Thymic stromal lymphopoietin (TSLP) is a cytokine that determines the survival, activation and expression of T lymphocytes, and TSLP is reported to have increased in the bronchial mucosa of COPD [78]. Silencing of IKKα protein can remarkably lower TSLP expression and IL-17A increases the cross-coupling between acetyl-histone H3 (Lys14) and Ikkα proteins [79]. As a member of IL-17 cytokine family, IL-17A can defend against bacterial infection [80]. HDAC2 can potentially differentiate T-cell into IL-17 producing cells [81]. IL-17A and HDAC2 expression in the lung tissue samples of COPD patients were correlated with collagen deposition and bronchial wall thickening [82]. This study suggests that the activation of HDAC2 can suppress IL-17A production and inhibit the development of airway remodeling in COPD [82]. Statins suppress the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA), involved in the cholesterol synthesis and subsequently anti-inflammatory effect through the post-translational modification of the small G-proteins Ras and Rho [83]. Statins lowers the risk of mortality, chest infections and hospitalization in COPD [84]. Matera *et al.* [85] reported that the statins restore expression and operation of depleted HDAC2. Type II alveolar epithelial cells (AECII) are essential for lung remodeling and development with AECII secreting inflammatory chemokines including Interleukin-8, monocyte chemoattractant protein-1 (MCP-1) and macrophage inflammatory protein-2α (MIP-2 α) [86]. Curcumin obtained from curcuma longa and is a yellow pigment which has anti-inflammatory properties [87]. Curcumin *via* modulating HDAC2 expression can restore corticosteroid and suppress inflammation chemokines in COPD [88] (Figure 1 summarized some of these therapeutic approaches). These findings show that HDAC2 can modulate COPD and some new therapeutic approaches can affect HDAC2 and inhibition of COPD. (Table 2).

Mirnas as a risk factor for COPD

Long noncoding RNAs (lncRNAs) are always spliced, capped and polyadenylated [89]. Studies have found that some lncRNAs can be potential biomarkers for the prognostication and diagnosis of COPD. Qu *et al.* [90] reported that the lncRNA ENST00000502883.1 was decreased in peripheral blood mononuclear cells in COPD patients, while Qi *et al.* [91] found that both lncRNAs including ENST00000447867 and NR-026690 were upregulated in COPD, and they can be noval biomarkers for diagnosis. Prolonged mechanical ventilation in the intensive care unit (ICU) can induce ventilator-associated pneumonia (VAP) [92]. Studies have revealed an association between COPD and higher VAP and ICU mortality [93] where TLR4 correlates with the risk of VAP. Zhao *et al.* [94] have found that miR-1236 can bind to 3′-UTR of TLR4 mRNA and pose the risk of VAP in COPD patients [94]. miR-206 was upregulated in skeletal muscle and plasma of COPD patients but was downregulated in gastric, lung and colorectal cancers [95,96]. Notch signaling has been demonstrated to possess high expression in the airway epithelium and be related to cell-fate determination such as apoptosis. Studies have reported reduced Notch signaling especially Notch3 in smokers with COPD. miR-206 expression was elevated in the lung tissues and inhibited the expression of Notch3 and VEGFA mRNAs in COPD group [97]. miR-34a and miR-199a-5p expression were remarkably higher in COPD lung tissues. Pulmonary endothelial cells and alveolar epithelial cells were higher in number in COPD lungs than normal lungs, and CSE triggered apoptosis time-dependently and dose-dependently in human umbilical vein endothelial cells [98]. Long *et al.* [99] illustrated that the expression of miR-34a can target Notch-1 gene in endothelial cells by binding to 3′UTR of Notch-1 involved in CSE. Dysfunction of Insulin-like growth factor (IGF) signaling, changing the number of ribosome and altering protein synthesis may resulted in growth cancer, atrophy and hypertrophy [100]. Protein turnover helps in providing amino acids as well as

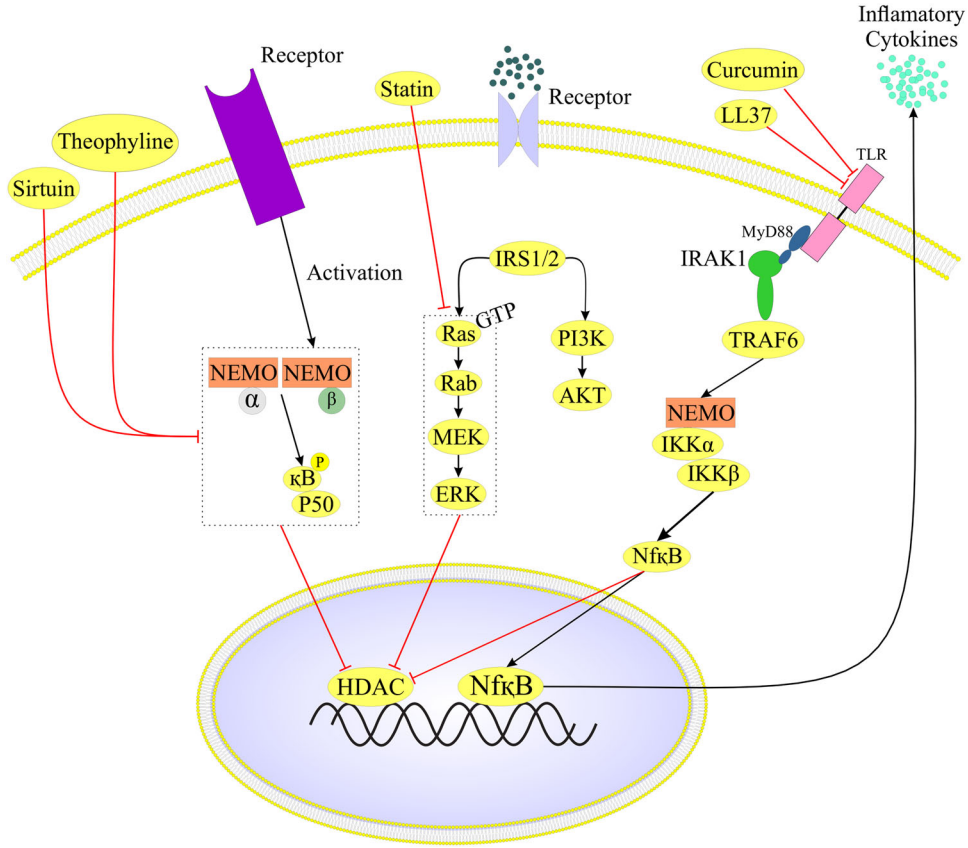

Figure 1. This figure demonstrates the therapeutic effect of some materials in COPD by targeting HDAC activity. Theophyline and Sirtuin by suppressing the NEMO pathway, Stain through preventing Ras activity and Curcumin, and LL-37 peptide *via* inhibiting TLR pathway can control HDAC activity and are new therapeutic approaches in COPD patients.

Table 2. Therapeutic approaches for COPD by targeting HDAC2.

Name	Effect	References
Trichostaina	Suppress skeletal muscle atrophy and histomorphological alteration	[52]
CARM1	Regeneration of airway epithelial cells	[57]
Sirtuins	Regulates NFkB and decrease inflammatory responses	[64]
LL-37	Inhibiting of pro-inflammatory cytokines activity	[71]
Theophylline	Downregulation of NFkBp65	[74]
Statin	Post-translational modification of the Ras and Rho	[83]
Curcumin	Restoring corticosteroid and suppressing inflammatory cytokines	[85]

energy and carbon as the building blocks for other tissues [101]. miRNAs regulate ribosome operation or the production of ribosomal proteins, and control protein synthesis pathways [102]. Expression of miR-424-5p in COPD patients inhibits protein synthesis causing the loss of muscle mass *via* inhibiting rRNA synthesis by regulating polymerase I pre-initiation complex formation [103]. The dysregulation of miRNAs in COPD and their potential effect on the development of COPD are summarized in Table 3.

Mirnas as a therapeutic approaches in COPD

As small non-coding RNAs (sncRNAs) that are not translated into proteins, miRNAs (micro RNAs) affects the progression of COPD [104]. Studies have shown the effect of miRNAs on lung diseases with others having identified miRNAs profiles involved in reducing and enhancing COPD development [105]. Both miR-320b and miR-150-5p have previously been proven as anti-cancer miRNAs and regulate cellular pathways, which plays a fundamental role in the development of lung cancer in COPD patients [106]. The expression of both miR-320 and miR-150-5p have two effect in COPD development: the prevention of the associated cancers with COPD such as lung cancer, and the suppression of inflammation and deceleration of tissue damage [107]. miR-146a downregulates inflammatory cytokines by suppressing Toll-like receptor (TLR) and IL-1 (Interleukin-1) signaling components Tumor Necrosis Factor (TNF) and IL-1 receptor-associated kinase (IRAK1), which are involved in negative feedback regulation of IL-8, IL-6 and IL-1β [108]. miR-146a with nanoparticles (NPs) activity decreased IRAK1 and TRAF6 in human adenocarcinomic alveolar basal epithelial cell line assisting respiration in the management and treatment of COPD [109]. One of the major features in COPD is chronic hypoxia and hypoxia-inducible factor-1 (HIF-1) is a regulator for responses to chronic hypoxia where HIF-1α plays a key role in COPD [110]. miR-186 has previously been found as one of the most critical determinates of cell

Table 3 /Dysregulation of miRNAs expression in COPD.

miRNAs	Expression level in COPD	Function	Reference
miR-146a	↓	dysregulates inflammatory cytokines by increasing Toll-like receptor (TLR)	[91]
miR-146a	↓	elevated IRAK1 and TRAF6 in human adenocarcinomic alveolar basal epithelial cell line	[92]
miR-186	↓	increased expression of HIF-1α and anti-apoptosis of inflammatory fibroblasts	[95]
miR-181a-2-3p	↓	Enhanced inflammasome activity and inflammatory responses	[99]
miR-197	↓	Dysregulation of the cell fate of both endothelial cells (ECs) and SMCs	[101]
miR-27-3p	↓	Increasing pro inflammatory cytokines andppARγ	[105]
miR-503	↓	augments VEGF release from lung fibroblasts	[108]
miR-483-5p	↓	activatingfibronectin and α-SMA and enhancing cell growth by abrogating TGF-β	[109]
miR-1236	↑	elevated risk of VAP in COPD patients	[119]
miR-206	↑	inhibiting expression of Notch3 and VEGFA mRNAs	[122]
miR-34a	↑	targeting Notch-1 gene in endothelial cells by binding to 3/ UTR of Notch-1	[124]
miR-199a-5p	↑	targeting Notch-1 gene in endothelial cells by binding to 3/ UTR of Notch-1	[116]
miR-424-5p	↑	inhibits the protein synthesis and loss of muscle mass	[128]
miR-183-5p miR-3177-3p miR-218-5p	↓	Negative correlation with severity of COPD and have been introduced COPD biomarkers	[112]

Hypoxia-inducible factor-1 (HIF-1), Toll-like receptor (TLR), endothelial cells (ECs), transforming growth factor-β (TGF-β), Ventilator-associated pneumonia (VAP), Chronic obstructive pulmonary disease (COPD).

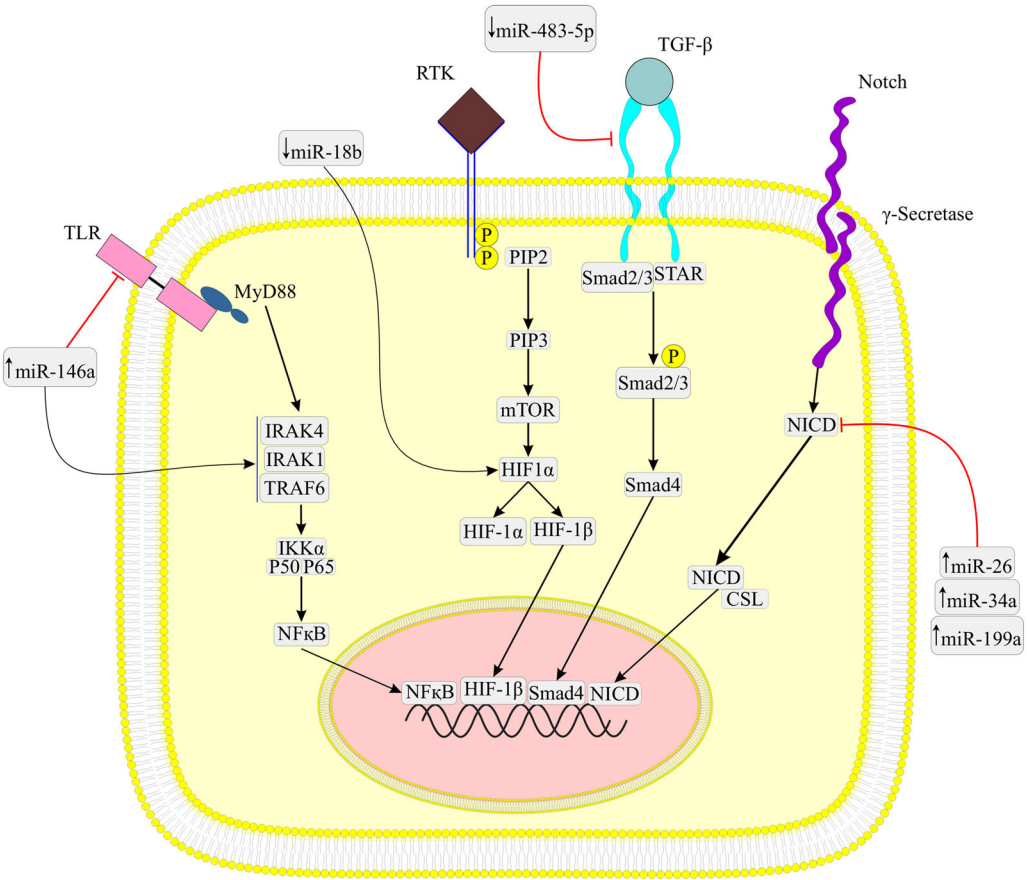

Figure 2. This figure shows dysregulation of various miRNAs correlated with COPD *via* different pathways. Upregulation of miR-146a by affecting TLR, IRAK4, IRAK1 and TRAF6 signaling pathway can exacerbate COPD. High expression of miR-26, miR-34a and miR-199a *via* inhibiting NICD pathways, downregulation of miR-483-5p through suppressing TGF-β and low expression of miR-18b by dysregulating HIF-1α operation can elevate COPD.

proliferation in different types of cancers [111]. Transfecting of miR-186 to lung fibroblast cell lines can affect HIF-1α and reduce the expression of HIF-1α, which results in the apoptosis of inflammatory fibroblasts [112].

One of the injurious components of cigarette smoke is Cadmium (Cd) that triggers airway inflammation and lung dysfunction in COPD [113]; Cd is also associated with the progression of COPD [114]. After human bronchial epithelial cells treated with Cd, the expression of miR-181a-2-3p was decreased and inflammasome activity and inflammatory responses were enhanced [115]. Thus, miR-181a-2-3p can be a therapeutic approach for COPD. The main cellular contributor to pulmonary vessel remodeling in COPD is intimal proliferation of dedifferentiated vascular smooth muscle cells (SMCs) [116]. In vessel remodeling, miRNAs regulate the cell fate of both endothelial cells (ECs) and SMCs (Smooth Muscle Cells) [117]. miR-197 expression was downregulated in COPD and is necessary for the acquisition of contractile markers in SMCs; it also correlated with an SMC contractile phenotype [118]. Alveolar macrophages (AMs) are immune cells which affect acute and chronic inflammatory responses [119]. AMs activation can release cytokines that play a role

in the pathogenesis of COPD [120]. Peroxisome proliferator-activated receptor gamma (PPARγ) is a member of the nuclear hormone receptor superfamily and can induce the inflammation of lungs [121]. miR-27-3p expression can regulate the production of pro-inflammatory cytokines and controlled TLR2/4 signaling through targeting the 3′-UTR sequences of ppARγ and suppressing ppARγ activation and also miR-27-3p in AMs [122]. It proved that the miR-27-3p can be a therapeutic method for COPD. The function of lung fibroblasts are altered in various ways in COPD, instigating changes in COPD through the production of lung fibroblasts including growth factors, fibronectin and inflammatory cytokines [123]. miR-503 expression was low in lung fibroblasts of COPD [124]. Vascular endothelial growth factors (VEGF) helps the removal of vasculature in COPD. Decreased expression of miR-503 in patients with COPD augments VEGF release from lung fibroblasts, so it can be a potential therapy for COPD [125]. miR-483-5p expression prevents α-smooth muscle actin (α-SMA), fibronectin and transforming growth factor-β (TGF-β) mediated decrease in cell proliferation [126]. miR-483-5p expression is found to be low in COPD that may protect miRNA in human lung cells through activating critical proteins such as fibronectin and α-SMA and enhancing cell growth by abrogating TGF-β [126]. Some miRNAs can be important biomarkers and target treatment for COPD [127]. Inflammation markers including dysregulation of miRNAs are associated with the severity of COPD [128]. miR-183-5p and miR-3177-3p were downregulated during the development and severity of COPD [129] and are critical biomarkers for the diagnosis of COPD. Reportedly, miR-218-5p and COPD severity have a negative correlation and Song *et al.* demonstrated the suppression of mi-218-5p in smokers or in those with COPD deficiency (Figure 2) [130].

Conclusion

As proved in a number of studies, dysregulation of DNA methylation in COPD-related genes, HDAC2 activity and miRNAs can trigger COPD disease. Cigarette smoke stimulates inflammatory responses and is a main factor for the progression of COPD. It alters epigenetic operation such as gene expression *via* changing DNA methylation, post-translational modifications of histone *via* changing HDAC2 activity and dysregulation of miRNAs-related COPD. Moreover, recent articles have shown the ability of some methods such as Sirtuins to regulate HDAC2 activity and have therapeutic effect in COPD. In more recent studies, miRNAs were demonstrated to decrease in COPD, and when bound with nanoparticles and transfected into human adenocarcinomic alveolar basal epithelial cell lines they can suppress COPD development as a therapeutic approach. Future studies are needed in a wider scope in both diagnosis and proposal of therapeutic approaches of the COPD.

Declaration of interests

Authors declare no conflict of interests.

ORCID

Leili Aghebati-Maleki http://orcid.org/0000-0002-0044-5961
Majid Ahmadi http://orcid.org/0000-0003-4787-5261

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