Epigenetic Optimization in Chronic Obstructive Pulmonary Disease (COPD)

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Abstract

As of 2020, chronic obstructive pulmonary disease (COPD), remains the third common principal cause of morbidity and mortality in adults. The various pathological processes governing COPD are chronic lung inflammation caused by increasing levels of environmental insults (particle matter, cigarette smoke, chemical fumes, ROS, etc.), inflammatory mediators, and protease. Alpha-1 antitrypsin deficiency causes lung tissue damage (apoptosis). The epigenetic mechanism includes post-translational methylation and acetylation of histone proteins and DNA, as well as modulation of miRNA production. In this chapter, we address all the recent research on the up- or down-regulation of methylation in various genes linked to COPD. A significant part of preventing and slowing the progression of COPD is played by inhibiting histone deacetylase activity, which is brought up by several variables and miRNAs. Additionally, some COPD treatment plans focus miRNAs and HDAC2 for therapeutic effects.

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6.1 Introduction

COPD is characterized by mucociliary dysfunction, pneumonia, chronic bronchitis, airway fibrosis, and alveolar disintegration. Because of the rising smoking epidemic, it is a prevalent chronic adult disorder, and will become the third biggest cause of mortality worldwide [1]. The pathophysiology of COPD is influenced by several variables, including chronic inflammation, the elastase/anti-elastase concept, proteinase-3 and cathepsin G-induced emphysema, apoptosis, oxidant-antioxidant imbalancing, and infectious repair [2]. With more than 7357 chemical components, 400 plus toxins, and 1014 reactive species, smoking of cigarette is the primary source of COPD and inflammatory processes via stimulating inflammatory cells declines lung function [3]. In COPD, the activation of inflammatory mediators such as IL1B, TNF-alpha, and TLR leads to the activation of NF-kB and other redox-sensitive epigenetic regulators. This, in turn, results in an upregulation of cytokines, cell adhesion molecules, and pro-inflammatory chemokines [4, 5]. An enzymatic modifications made to DNA proteins such as histone and others post-translationally followed by protein biosynthesis without altering the primary set of genes is called epigenetic modification [6]. A gene's expression may be influenced by DNA and histone methylation. DNA methylation is one significant epigenetic technique that alters the chemical structure of the DNA and controls transcription by interacting with microRNA and histone modification [7]. The post-translational modifications that affect the histone proteins include phosphorylation, methylation, ubiquitination, sulfonation, and acetylation. By adding methyl groups to the cytosine residues in loci, DNA methylation, the primary method of epigenetic control, is carried out by enzymes of the DNA ethyl transferase (DNMT) class [8, 9]. In CpG island gene promoter regions, DNA hypomethylation stimulates transcription, whereas DNA hypermethylation typically results in gene silencing [10]. Hypermethylation of DNA in CpG island gene promoter regions frequently cause gene silencing, whereas hypomethylation causes transcriptional activation of DNA. One of the essential elements of epigenetic mechanisms is histone modifications, which produce hereditary changes in gene expression without altering the DNA sequence [11] (Fig. 6.1).

The important functional unit of chromatin, is nucleosome, is composed of a core of two molecules of H2A, H2B, H3, and H4 each histone, which is surrounded by approximately 150 base pairs of DNAs [12]. The histone modifications H3K4me3, H3K9me3, and H3K27me3 are crucial for gene regulation. H3K4me3 and the initiation of gene expression are related, whereas H3K27me3 and H3K9me3 are related to organic phenomenon. The expression of protein-coding genes is strictly regulated by ncRNAs, which do not act as templates for protein synthesis [13]. Non-coding RNAs, often known as microRNAs, are another type of post-transcriptional regulator of gene expression by degradation of mRNA and disruption. RNA polymerases can create miRNAs, which are 21–23 nucleotides long and can be produced by transcription of parent RNA [14]. Non-coding RNA (ncRNA) controls the expression of protein-coding genes in a significant way. Non-coding RNA are made of small ncRNAs like microRNA and long ncRNAs [15]. Studies show that miRNAs regulate maximum of the protein-coding genes. To boost

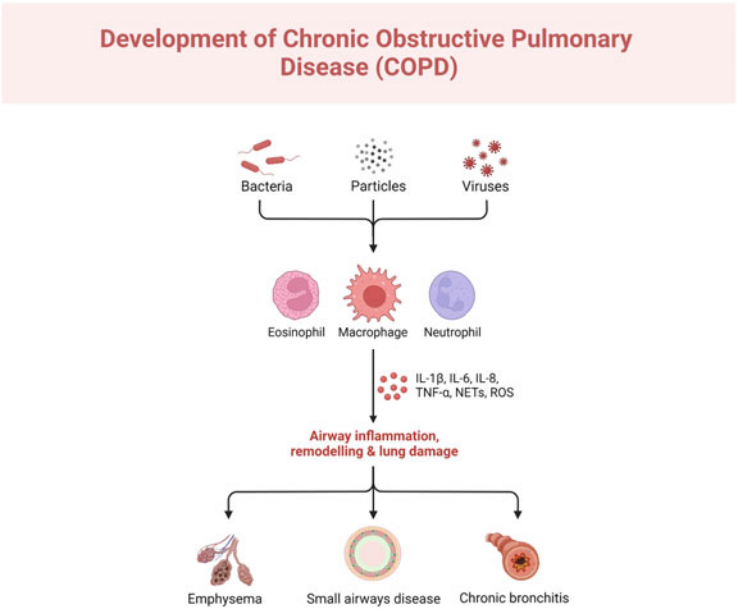

Fig. 6.1 Development of COPD

fragmentation or reduce translation, respectively, they do this by binding to the 3'-UTR or 5'-UTR of the nucleotide. While lncRNA are connected to genetic variations linked to disease, microRNA act as a negative regulator of gene expression [16].

6.2 Inheritance and COPD

Gene expression can alter in a heritable way through the modification of histones or DNA sequences. It has been shown that epigenetic alterations in COPD include abnormal inflammatory gene activity, aberrant DNA methylation, aberrant histone acetylation and deacetylation, and dysregulated miRNAs [17, 18]. In COPD patients' and smokers' lungs, epithelial cells and macrophages may react differently to cigarette smoke and oxidants due to epigenetic events. Asthma and COPD are chronic lung disorders that may be exacerbated or prevented by changes in DNA methylation, histone acetylation, and miRNA activity [19, 20]. Cigarette smoke extract (CSE) increased COPD by aggravating genetic modifications, particularly those in DNA of mitochondria. Investigations reveal that the CpG region of COPD patients (CpG) site displays a range of methylation signals in response to air pollution [21].

6.3 Genetic Methylation and COPD

DNA methylation is an epigenetic mechanism which further causes inactivation of pro-inflammatory genes and results in development of COPD. Pleural space macrophages and epithelium from COPD patients have been found to have DNA methylation of the genes of proinflammatory cytokines [22]. The existence and progression of COPD are discovered to be strongly influenced by DNA methylation; cigarette smoking can also change DNA methylation by inducing inflammatory responses and resulting diseases like COPD. The division of innate and adaptive immunity, along with the identification and abolition of pathogens, are all important functions of lung macrophages, which are innate immune cells [23]. Studies have shown physiological differences between the upper and lower parts of the lung in ventilation and respiration, while COPD typically appears as upper lobe predominance [24]. Several alveolar macrophage genes, like HSH2D, have been shown to have 95 CpG sites with significant methylation dysregulation via ventilation and oxygen variation between the upper and lower lobes. Similar mechanism is seen in SNX10/CLIP4 (Sorting Nexin 10) and TYKZ genes [25]. Mitochondrial transcription factor A is a key player in the pathogenesis of disorders like immune responses, necrosis, and inflammation. The mtTFA expression in the skeletal muscles is markedly lower in COPD patients. To regulate mtDNA nucleotide sequence and mitochondrial transcription initiation, mtTFA binds to the promoter regions of the HSP1 and LSP of mtDNA [26, 27].

Smoking increased the mtTFA promoter's hypermethylation, which led to the development of COPD. There is a link between air pollution and various lung diseases, including COPD [28]. Promoters of air pollution, such as toxic particles or gases, can cause epigenetic alterations, including altered DNA methylation [29]. Air pollution promoters can cause epigenetic changes, including altered DNA methylation. Air pollutant of size less than 10um are called particle matter 10 (PM10). Air pollutants such as PM10 and NO2 lead to the dysregulation of methylation at target genes like ARID5A (AT-Rich Interaction Domain 5 A), NEGR1 (Neuronal growth regulator 1), RPL5 (Ribosomal Protein L5), FOXl2 (Forkhead Box 12), CPLX1 (Complexin 1), STON1, and others [30, 31]. PM10 is closely associated with 12 differentially methylated probes (DMP) and 27 differentially methylated probes (DMR) while NO2 is associated at 57 DMRs and 45 DMPs in CpG region [32]. Fibroblasts can be found in a variety of endothelium tissues, including the adventitia of the vascular system, the alveolar ducts, and the elderly respiratory muscles. Lung fibroblasts are important for ECM homeostatic mechanisms, lung recovery, and cell of stem repairs [33]. According to TGFß response, rate of proliferation, and ECM, airway and parenchymal fibroblasts behave differently in COPD patients (ECM). A total of six hundred fifty-two regions with differential methylation, some of which are within gene regions [34]. In reply to TGFB and physiological extracellular matrix, the targeted genes HLA-DP1, RPH3AL, TMEM44, WNT3A, and HLA-DRB5 experience dysregulation of methylation by airway and parenchymal fibroblasts. HLX genes, which are hypomethylated in NXN (Nucleoredoxin) genes but hypermethylated in COPD,

have at least three CpG sites, according to research that showed 44 DNA differentially methylated areas [35, 36]. Variants in the expression of the SERPINA1 gene may raise the risk of COPD and its related lung function abnormalities. SERPINA1 expression of gene alternatives might increase COPD hazard and linked function of lung phenotypes [37]. In smoking adults with COPD, there is altered methylation at two CpG sites within the SERPINA1 gene. This abnormal methylation may lead to excessive mucus secretion and goblet cell metaplasia, contributing to the development of COPD [38].

Human airways' tracheal epithelium consists of ciliated, basal, neuroendocrine, Clara cells, and basal cells. FoxA2 and transcription factors are both forkhead box proteins. Genes encoding SAM-pointed domains that include ETS-like factors (SPDEF) are two essential controllers of goblet cell development [39]. SPDEF is accountable for both mucus production and the development of goblet cells. On the other hand, dysregulated goblet cell differentiation in the lungs involves targeted genes regulated by FoxA2 [40]. The foxA2 promoter has 11 CpGs that are hypomethylated, while the SPDEF promoter has 6 CpGs that are hypomethylated. Sphingosine-1 phosphate (S1P) promotes maturation of macrophages and is essential for their phagocytosis [41]. In COPD, alveolar macrophages are associated with dysregulated S1P gene expression. S1P methylation in smokers is lower than in non- or ex-smokers. In individuals with COPD and smokers, targeted genes such as GABRB1, NOS1AP, TNFAIP2, and BID show hypermethylation compared to the healthy group [42]. The genes SERPINA1 and AHRR (Aryl-Hydrocarbon Receptor Repressor) have considerably lower levels of methylation in people with COPD and smokers [43]. The IGF system, particularly IGF1 and IGF1R, is essential for lung development. Smoke causes a CpG site-specific hypomethylation in the IGF1R promoter leading to suppression of lungs development [44]. Cigarette smoking can disturb DNA methylation, potentially initiating COPD. Several genes, including GPR126, three cholinergic receptors (CHRND, CHRNB1, and CHRNB2), EPHX1, and three glutathione S-transferases, exhibited hypermethylation. Conversely, only 3% of the genes, including KSR1, showed hypomethylation in response to cigarette smoke [45, 46].

6.4 HDAC2 Deregulation and COPD Induce Histone Modification

HDACs and HAT coenzymes jointly regulate activation (by histone acetylation) and silencing (by deacetylation), which has a significant effect on the emergence of inflammation in COPD [47]. Lysine residues are used to acetylate histones H3 and H4. Studies have shown that in individuals with COPD and the resulting inflammation, the balance between acetylation and deacetylation can change in favor of acetylation [48]. Smoke from cigarettes can cause acetylation of H3 in macrophages and human lung tissue. Histone deacetylases (HDACs) control the amount of histone acetylation to control protein function and gene transcription. HDACs control numerous major macromolecular complexes and epigenetic regulation during

biological processes [49]. Previous studies have demonstrated that inhibiting HDAC1 and HDAC2 during the perinatal period in muscle tissue causes muscle fiber degeneration and mitochondrial abnormalities, which lead to the death of some mouse pups. Mice exposed to tobacco smoke have increased levels of HDAC1/2 (CS) [50]. HDAC blocker can be used to treat COPD patients by decreasing HDAC1/2, which ultimately prevents muscle fiber degeneration and histomorphological changes [51]. Trichostaina (TSA) comes under the category of HDACs blocker. Protein arginine methyl transferases (PRMTs), found in both histone and non-histone proteins, add a methyl group to arginine residues as the second significant histone alteration [52]. Coactivator-associated arginine methyl transferase 1 (CARM1) affects the regulation of gene expression by demethylating arginine residues in several non-histone proteins, including histone H3 and many others. CARM1 expression is increased in healthy epithelial cells but downregulated following epithelial cell damage in COPD [53, 54]. Therefore, via controlling cellular senescence, the regeneration and repairing of airway epithelial cells depend on CARM1. Lowering HDAC activities allows PM, such as fine and semi ultra-fine particles (UFP), to enhance the HAT/HDAC ratio [55]. The COPD-affected human bronchial epithelial (DHBE) group and the group stated above both had significant levels of H3K9 histone acetylation. Two key factors to limit inflammation in the airways and lung parenchyma in COPD are oxidative stress and cigarette smoking [56]. Oxidative stress can trigger the activation of nuclear factor kB (NFkB), which raises levels of pro-inflammatory factors and causes COPD. Sirt1 (Silent Information Regulator 1) belongs to the family of class 3 histone/protein deacetylases and is associated with inflammation, cell aging, senescence, as well as COPD/emphysema [57]. Research has revealed that SIRT1 controls NFkB and lessens inflammatory reactions. In COPD, erythromycin increased SIRT1 expression, which in turn reduced NFkB acetylation and pro-inflammatory cytokines. FoxO3 is a member of the Fox family, and it has been shown to decrease NFkB activity in COPD patients when SIRT1 and foxO interact [58]. CSE interferes with the function of SIRT1/FoxO3, which in turn dysregulates the NFkB activity and increases inflammatory responses. Glucocorticoid-dependent anti-inflammatory effect depends on reducing HDAC2, yet when HDAC2 is lowered, oxidative stress and inflammation increase. Smoking elevated oxidative stress and promoted COPD glucocorticoid resistance, both of which were associated with higher acetylation (HDAC2). A peptide called LL-37/hCAP18 has the power to inhibit the C-Jan N-terminal kinases (JNK), the AKt phosphorylation, and the activity of pro-inflammatory cytokines in macrophages [59, 60].

According to research, LL-37 boosted HDAC2 activity and expression in COPD patients via blocking the PI3K/AKt pathway. A phosphodiesterase isoenzyme inhibitor called theophylline reduces activity by preventing pro-inflammatory transcription factor expression and its entry into the nucleus. In rodent skeletal muscle cells, tobacco smoke can increase NFkBp65 polypeptide, TNF-a, and IL-8 levels in COPD [61]. By increasing HDAC2 expression and decreasing pro-inflammatory transcription factor expression, theophylline decreases inflammation in COPD patients (NFkBp65). Inhibitor kappa B (IkB) is phosphorylated and degraded to activate

NFkB, which causes transcription of NFkB-dependent genes [52, 62]. The pulmonary vasculature of COPD patients has been reported to have higher levels of the cytokine thymic stromal lymphopoietin (TSLP), which influences T cell survival, activation, and expression [62]. The pairing between IKKa and acetyl-histone H3 (Lys14) proteins is promoted by IL-17A, and IKKa protein silencing can drastically lower the expression of TSLP. A cytokine that helps combat bacterial infection is called IL-17A. HDAC2 may be involved in the differentiation of T cells that produce IL-17 [63]. In COPD patients' lung tissue samples, it was found that the expression of lymphocyte-associated protein and histone deacetylase was associated with the accumulation of collagen and thickening of the bronchial walls [64]. This study shows that in COPD patients, activating deacetylase enzyme can decrease lymphocyte-associated protein production and stop airway remodeling. Statins decrease the formation of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA), which is involved in the production of cholesterol, through the post-translational modification of the small G-proteins Ras and Rho [53, 65]. In patients with COPD, statins reduce the risk of death rates, respiratory infections, and hospitalization. The statins restore the expression and operation of weakened HDAC2 [66]. Type II alveolar epithelial cells (AECII), which also release inflammatory chemokines like interleukin-8, monocyte chemoattractant protein-1 (MCP-1), and macrophage inflammatory protein-2a, are necessary for lung remodeling and development (MIP-2 a) [67]. *Curcuma longa* plant produces curcumin a pale-yellow pigment with anti-inflammatory properties. In COPD, curcumin can restore corticosteroids and reduce inflammatory chemokines by modulating the expression of HDAC2 [68].

6.5 mRNAs as a COPD Disease Risk

Long non-coding RNAs (lncRNAs) undergo continuous processes of splicing, capping, and polyadenylation. Some lncRNAs may act as indicators for the evaluation and prognosis of COPD, according to studies [69]. Peripheral blood mononuclear cells from COPD patients have lower levels of the lncRNA ENST00000502883. Enst00000447867 and NR-026690, two lncRNAs that may serve as diagnostic indicator (biomarkers) for COPD, were both elevated in the disease. Prolonged artificial breathing can cause ventilator-associated pneumonia (VAP) in critical care unit's patients [70]. According to studies, TLR4 and the risk of VAP are correlated, and COPD is linked to increased rates of VAP and ICU mortality. In COPD patients, miR-1236 can enhance the prevalence of VAP by binding to the 3'-UTR of the TLR4 mRNA [71]. Patients with COPD had miR-206 that was elevated in their skeletal muscle and plasma, whereas it was dysregulated in cases of gastric, lung, and colorectal cancer. It has been shown that Notch signaling is highly expressed in the airway epithelium and is involved in controlling cell fate, including apoptosis [72]. Reduced Notch signaling, particularly Notch 3, has been observed in smokers with COPD, according to studies. The transcription of miR-206 was elevated in the lung parenchyma of the COPD group, which suppressed the transcription of the mRNAs for Notch 3 and VEGFA. In COPD lung tissues,

miR-34a and miR199a-5p expression was noticeably higher [73]. Alveolar epithelial cells and pulmonary endothelial cells were more numerous in COPD-affected lungs than in healthy lungs, and CSE caused human umbilical vein endothelial cells to undergo apoptosis in a time- and dose-dependent manner [74]. The binding of the miR34a to the 3/UTR of the CSE-related Notch-1 gene can target the Notch-1 gene in endothelial cells. Growth cancer, atrophy, and hypertrophy can all be caused by impaired insulin-like growth factor (IGF) signaling, which also affects the quantity of ribosomes and protein synthesis [75]. As building blocks for other tissues, amino acids, energy, and carbon are all provided by protein turnover. In addition to controlling protein synthesis pathways, miRNAs also regulate ribosome function or the synthesis of ribosomal proteins. MiR-424-5p expression in COPD patients prevents protein synthesis by regulating polymerase I, which lowers muscle mass [76].

6.6 miRNAs as a COPD Treatment Strategy

miRNAs (micro RNAs) are short non-coding RNA which are not translated into proteins; they have a certain impact on the development of COPD. Numerous studies have demonstrated the impact of miRNAs on lung disorders which shows a correlation between specific miRNA profiles and both the prevention and acceleration of the development of COPD [77]. The control of cellular pathways has a significant impact on lung cancer development in COPD patients by miR-320b and miR-150-5p, two miRNAs that have been formerly proved to be anti-cancer. The expression of miR-320 and miR-150-5p has two effects on the onset of COPD: it protects the cancers linked to COPD, such as lung cancer, and it lowers inflammation and tissue damage. Inflammatory cytokine production is suppressed by miR146a [78, 79]. TNFa and proinflammatory mediators (IRAK1) are responsible for the negative regulation of the Toll-like receptor (TLR) and Interleukin-1 (IL-1) signaling components IL-8, IL-6, and IL-1b. In human adenocarcinoma alveolar basal epithelial cell line, miR146a with nanoparticles (NPs) activity lowered IRAK1 and TRAF6, aiding breathing in the management and treatment of COPD. One of the main traits of COPD is persistent hypoxia, and hypoxia-inducible factor-1 (HIF-1) regulates how the body reacts to chronic hypoxia, where HIF-1a is significant in COPD [80]. Previous research has identified miR-186 as one of the most important factors influencing cell proliferation in many malignancies. When lung fibroblast cell lines are transfected with miR-186, HIF-1a is impacted and its expression is reduced, which causes inflammatory fibroblasts to apoptosis. Cadmium (Cd), one of the harmful substances in cigarette smoke, causes lung impairment and inflammation in persons with COPD. Cd is linked to the development of COPD as well [53, 61, 70]. After exposure to Cd, human bronchial epithelial cells' transcription of MiR-181a-2-3p was downregulated, although proinflammatory activity and inflammatory reactions were both elevated. Consequently, miR-181a-2-3p may be used as a treatment for COPD. Intimal proliferation of dedifferentiated vascular smooth muscle cells in COPD is the key cellular factor contributing to pulmonary artery

remodeling (SMCs) [67]. During vascular remodeling, miRNAs regulate the fate of both endothelial cells (ECs) and smooth muscle cells (SMCs). MiR-197 transcription must be negatively regulated for COPD to establish contractile activity. There is a correlation between SMC contractile markers and their respective phenotypes. Immune cells called alveolar macrophages (AMs) influence both acute and chronic inflammatory responses [70].

6.7 Conclusion

Cytokines that are involved in the pathophysiology of COPD can be released when AMs are activated. Lung inflammation can be brought on by the nuclear hormone receptor subfamily member peroxisome proliferator-activated receptor gamma (PPARc). By concentrating on the 3′-UTR regions of PPARc and inhibiting PPARc activation, miR-27-3p expression can restrict the production of pro-inflammatory cytokines and regulated TLR2/4 signaling. It demonstrated that miR-27-3p can be used as a COPD treatment strategy. The functionality of lung fibroblasts is altered in a variety of ways by the production of lung fibroblasts, including growth factors, fibronectin, and inflammatory mediators. COPD lung fibroblasts expressed miR-503 less highly. The loss of vasculature in COPD is aided by vascular endothelial growth factors (VEGF). Reduced expression of miR-503 in COPD patients increases the release of VEGF from lung fibroblasts, suggesting that it may be used as a COPD treatment. Expression of miR-483-5p prevents the suppression of cell development brought on by a-Smooth muscle actin (a-SMA), fibronectin, and transforming growth factor-b (TGF-b). Some miRNAs may serve as crucial indicator for COPD therapy targets. COPD severity is linked to inflammation indicators, including dysregulation of miRNAs. MiR-183-5p and miR-3177-3p, which are important biomarkers for the diagnosis of COPD, were downregulated during the onset and disease progression. It has been shown that miR-218-5p is suppressed in smokers or people with COPD insufficiency, and there is a reported negative association between miR-218-5p and the severity of COPD.

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