Literature Review

Exploring Epigenetic Landscapes in COPD: Therapeutic Implications and Recent Insights

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Abstract

Chronic Obstructive Pulmonary Disease (COPD) is a leading cause of global mortality, primarily driven by an abnormal inflammatory response to harmful particles and gases. This review explores the epigenetic mechanisms underlying COPD pathogenesis and their therapeutic implications. A comprehensive literature review was conducted, analyzing recent findings on DNA methylation, histone modifications, and noncoding RNAs (ncRNAs) in COPD. Key studies highlighting the impact of these epigenetic changes on inflammation, cellular responses, and disease progression were evaluated. Our review highlights that epigenetic modifications, such as DNA methylation and histone modifications, significantly impact gene expression without altering the DNA sequence. Cigarette smoking has been shown to influence both DNA methylation and histone acetylation, leading to inflammatory responses and the exacerbation of COPD. These modifications contribute to chronic inflammation and disease progression, with alterations in histone acetylation, methylation, and phosphorylation playing critical roles in COPD pathogenesis. The interplay between epigenetic changes and environmental factors, particularly tobacco smoke, reveals a complex mechanism driving COPD progression. Aberrant gene expression linked to these epigenetic modifications suggests potential disease severity and progression biomarkers. Targeting these alterations offers novel therapeutic strategies. Emerging treatments, such as quercetin and theophylline, promise to restore normal cellular functions and effectively manage COPD. Future research should focus on elucidating these mechanisms further and developing targeted therapies to mitigate the impact of epigenetic modifications on COPD.

Keywords: chronic obstructive pulmonary disease, DNA methylation, epigenetics, histone modifications, therapeutic strategies

INTRODUCTION

COPD, recognized as the third leading cause of mortality globally by 2020, is characterized by mucociliary dysfunction, lung inflammation, airway fibrosis, alveolar destruction, and chronic

bronchitis with mucus hypersecretion.[1–3] Affecting millions worldwide, COPD significantly contributes to both morbidity and mortality, representing a substantial health burden with high associated healthcare costs.[4]

According to the World Health Organization (WHO), the number of COPD cases is projected to increase by 30%, reaching approximately 4.6 million people by 2030.[5] This rising prevalence is primarily driven by continued tobacco use, the major risk factor for COPD, along with indoor air pollution, occupational exposures, and an aging global population. Cigarette smoke, containing over 4,700 chemical compounds and 10^{14} free radicals/oxidants, plays a central role in COPD pathogenesis and its associated inflammatory responses.[6]

COPD is a complex disease influenced by genetic predispositions, environmental exposures, and epigenetic modifications within a developmental context. Recent studies emphasize the critical yet underexplored role of genetic susceptibility, including epigenetic changes, in the development and progression of COPD. Epigenetic mechanisms, such as DNA and RNA methylation, histone modifications, and noncoding RNAs, modulate the response of lung epithelial cells and macrophages to harmful substances, including cigarette smoke and oxidants.[7]

These epigenetic modifications, such as DNA and RNA methylation, histone modifications, and noncoding RNAs, influence gene expression temporally and spatially without altering the underlying DNA sequence.[8] For instance, cigarette smoking induces DNA methylation, which in turn activates inflammatory pathways contributing to COPD pathogenesis.[9]

Despite advancements in understanding COPD, the disease remains incurable. However, symptomatic treatments can help mitigate disease progression and improve patient outcomes. This review aims to provide a comprehensive overview of current evidence regarding epigenetic changes associated with COPD. Furthermore, understanding these epigenetic alterations could pave the way for personalized treatment approaches, potentially reducing the burden of chronic lung diseases.

EPIGENETICS AND PULMONARY DISEASES

Epigenetic regulation of gene expression and protein synthesis involves a range of well-established mechanisms essential for normal development and cellular adaptation to maintain homeostasis. These mechanisms ensure that genetic information is appropriately expressed in response to environmental and physiological changes.[10]

Epigenetics encompasses inheritable chromatin structure and biochemistry alterations that do not involve changes to the DNA sequence itself. These processes affect both normal and disease states by modulating gene expression. The primary epigenetic mechanisms extensively studied include DNA methylation, histone

modifications, and non-coding RNAs (ncRNAs).[11]

Research increasingly highlights the role of epigenetics in developing various pulmonary diseases, such as COPD and asthma. These conditions emerge from complex interactions between environmental factors, such as cigarette smoke and pollution, and genetic susceptibility, leading to altered gene expression without changes in the DNA sequence. Epigenetic modifications regulate crucial processes like inflammation, fibrosis, and airway remodelling in the lungs. For example, exposure to cigarette smoke has been shown to induce changes in histone modification patterns and DNA methylation, contributing to chronic inflammation and oxidative stress.[12]

Reduced histone deacetylases (HDACs) activity in COPD has been associated with intensified inflammatory responses and decreased effectiveness of corticosteroids.[3,13] Research indicates that targeting epigenetic modifications through HDAC inhibitors or DNA methylation modulators could be a promising therapeutic strategy for addressing these abnormal gene expression patterns.[3]

EPIGENETIC MECHANISM OF COPD

COPD is a complex disorder influenced by a combination of genetic factors, environmental exposures, and epigenetic changes within a developmental framework. Investigating the epigenetic basis of COPD can offer an unbiased assessment of key molecular elements involved in its pathobiology, potentially revealing new insights into the mechanisms that drive the disease. COPD is a complex and varied condition within the lung that involves damage to the lung parenchyma, leading to a reduction in elastic recoil (emphysema) and disease affecting the small airways.[14] COPD is characterized by progressive airflow obstruction, which may result from emphysema-related damage to lung tissue, fibrosis and destruction of small airways, and/or excessive mucus production typical of chronic bronchitis.[2]

Smoking is the most significant risk factor for COPD, with research highlighting its impact throughout an individual's life, from prenatal exposure to old age, and showing that smoking induces extensive epigenetic changes that can persist long after cessation.[15] In addition to smoking, exposure to other harmful inhalants, such as biomass combustion products, is also a well-documented risk factor for COPD.[2] The review underscores how epigenetic modifications lead to aberrant gene expression that drives inflammatory and fibrotic processes in COPD.

DNA Methylation

DNA methylation is one of the most extensively studied epigenetic mechanisms due to its crucial role in regulating gene expression. This modification involves the covalent attachment of a methyl group to the 5' carbon of cytosine within cytosine-phosphate-guanine (CpG) dinucleotide sequences in the genome, influencing

gene regulation.[16] DNA methylation is catalyzed by DNA methyltransferases (DNMTs) and is essential for various biological processes, including gene silencing, imprinting, and X-chromosome inactivation. Aberrations in DNA methylation are linked to several diseases, including COPD.[17]

Variations in DNA methylation are linked to COPD status and can impact gene expression for specific genes. The methylation profiles differ between airway and parenchymal fibroblasts, indicating that DNA methylation affects disease pathology differently in these distinct lung tissue types.[14] The reversibility of DNA methylation, influenced by the duration and intensity of smoking exposure, suggests that it could serve as a potential biomarker for COPD.[18]

This altered methylation status reduces the expression and activity of cyclo-oxygenase-2 (COX-2) in pulmonary vascular endothelial cells, potentially contributing to endothelial apoptosis in COPD.[19] Recent research suggests that the apoptosis of structural cells in the lung is a crucial upstream event in COPD pathogenesis.[20]

Studies have demonstrated that genes such as COX-2 undergo hypermethylation, leading to chronic mucus hypersecretion, airway fibrosis, and persistent inflammation in the lungs.[9] This dysregulation exacerbates the inflammatory response and contributes significantly to COPD progression.[21,22] Prostacyclin, another cyclo-oxygenase product, may offer protection against emphysema by slowing apoptosis in the lung's microvascular endothelium.[23]

In COPD, cigarette smoking is a major driver of abnormal DNA methylation. The harmful chemicals in cigarette smoke induce the methylation of genes related to inflammation, oxidative stress, and apoptosis.[20] The epigenetic changes induced by cigarette smoke can persist even after smoking cessation, underscoring the long-term impact of smoking on lung tissue. These alterations affect gene expression and contribute to corticosteroid resistance and chronic airway remodelling, complicating disease management.[16]

Differentially methylated sites (DMSs) can be integrated into current models for predicting COPD risk, offering more accurate predictions than traditional clinical variables alone. DMSs from peripheral blood have both predictive and clinical significance, making blood a promising tissue for biomarker development due to its accessibility and the possibility of repeated sampling.[16] Understanding DNA methylation's role in COPD pathogenesis could lead to potential therapeutic strategies, such as targeting DNMTs or reversing abnormal methylation patterns to alleviate inflammation and slow disease progression.[24]

Armstrong et al identified specific CpG loci with significant methylation differences (such as HSH2D [Hematopoietic SH2 Domain Containing], SNX10 [Sorting Nexin 10], CLIP4 [CAP-Gly domain containing linker protein family member 4], and TYK2 [Tyrosine Kinase

2]), which are linked to genes involved in immune response, inflammation, and metabolism.[1,25]

These epigenetic modifications may contribute to the functional heterogeneity of macrophages, influencing processes such as pathogen defense, inflammatory regulation, and energy metabolism in the lungs.[1,25] Methylation of the chromosome 10 open reading frame 11 (C10orf11) gene, which has been linked to COPD through genome-wide association studies (GWAS), was detected in the airway epithelial cells and lung tissues of smokers who developed COPD.[26]

Cigarette smoking can lead to methylation changes in the promoter region of the mitochondrial transcription factor A (mtTFA) gene. Peng et al discovered that DNA methylation levels of the mtTFA promoter were significantly higher in individuals with COPD, which resulted in reduced mtTFA mRNA expression in the lungs.[27]

In cigarette smoke extract (CSE)-treated human umbilical vein endothelial cells (HUVECs), both mtTFA mRNA and protein expression were similarly downregulated due to hypermethylation of the mtTFA promoter. This cigarette smoke-induced hypermethylation is associated with the initiation and progression of COPD. The study suggests that demethylation agents targeting mtTFA hypermethylation, such as the methylation inhibitor 5-aza-2'-deoxycytidine (AZA), could restore mtTFA expression and potentially offer a novel therapeutic approach for COPD.[27]

The primary risk factor for COPD is inhaling harmful particles, such as cigarette smoke, which damages the airway epithelium and initiates inflammation. In COPD patients, cigarette smoke induces hypomethylation of Aryl Hydrocarbon Receptor Repressor (AHRR) in airway epithelial cells, leading to increased AHRR expression and reduced aryl hydrocarbon receptor (AHR) expression, impairing its protective effects. Increased expression of AHRR in airway epithelial cells could result in disrupted mitochondrial function and apoptosis/necroptosis induced by cigarette smoke, potentially leading to uncontrolled cell death.[28]

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Glutathione (GSH) is one of the antioxidants that protect the airway epithelium from damage, with its synthesis regulated by glutamate-cysteine ligase (GCLC). GSH levels decrease quickly in the lungs, plasma, and liver following cigarette smoke exposure in both mice and humans.

Cigarette smoke-induced hypermethylation of the GCLC promoter is linked to the onset and progression of COPD. This finding suggests that developing demethylation agents targeting GCLC hypermethylation could offer a new approach to COPD intervention.[29]

Specific changes in DNA methylation are linked to pollutants such as particulate matter (PM) and nitrogen dioxide (NO_2). The findings suggest that air pollution may influence disease development through changes in DNA methylation, providing insights into the biological mechanisms underlying pollution-related health risks. These epigenetic modifications are associated with genes involved in inflammation, oxidative stress, and cardiovascular and respiratory diseases.[30]

Song et al discovered that there is hypomethylation at 11 CpG sites in the Forkhead box protein A2 (FoxA2) promoter and 6 CpG sites in the SAM Pointed Domain Containing ETS Transcription Factor (SPDEF) promoter. The involvement of SPDEF and FoxA2 in mucus hypersecretion in COPD suggests that targeting these factors through epigenetic inhibition could provide new strategies for controlling mucus hypersecretion.[31]

Histone Modification

Various histone modifications, including acetylation, methylation, and phosphorylation, play significant roles in regulating gene expression. In COPD, smoking alters these histone marks, impacting inflammatory responses and disease progression.[21] An imbalance between histone acetylation and deacetylation affects nucleosomal structure during the transcription of inflammatory cytokine genes, which can result in altered gene expression profiles in smokers who are at risk of developing COPD.[18]

Histone Acetylation and Deacetylation

The release of pro-inflammatory cytokines depends on the activity of the transcription factor nuclear factor kappa B (NF-κB). This factor works in conjunction with co-activators like p300 and cAMP-response element binding protein (CREB), which possess histone acetyltransferase (HAT) activity, to promote gene transcription.[18]

Histone acetyltransferase enhances gene transcription by promoting the expression of pro-inflammatory factors involved in pathways such as mitogen-activated protein kinase (MAPK), Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), and Signal Transducer And Activator Of Transcription (STAT), leading to inflammatory responses in epithelial cells. HAT activity modifies chromatin structure, making it more accessible to transcription factors and amplifying the inflammatory response seen in diseases like COPD.[1–4]

In the context of cigarette smoke exposure, a major risk factor for COPD, HAT-mediated acetylation exacerbates lung inflammation by increasing the expression of cytokines and chemokines. This highlights the potential for targeting HATs as a therapeutic strategy to reduce

chronic inflammation in respiratory diseases.[1–4]

HDACs are classified into several groups. They play a key role in gene regulation by removing acetyl groups from histones, resulting in chromatin condensation and transcriptional repression. Smoking has been shown to alter HDAC function, particularly reducing HDAC2 activity, which amplifies the inflammatory response and contributes to COPD progression.[18] Oxidative stress further exacerbates this effect by inhibiting HDAC2 activity. Chronic oxidative stress leads to both reduced HDAC2 activity and expression, which in turn enhances inflammation and corticosteroid resistance, complicating COPD management.[32]

Histone Methylation

Histone methylation plays a critical role in gene regulation, with specific patterns either activating or repressing gene expression. Altered methylation patterns in diseases like COPD can contribute to disease progression by modulating the expression of genes involved in inflammation and lung function.[1–3] Methylation of histone lysine or arginine residues leads to distinct, and sometimes even contradictory, functional outcomes. Additionally, the same lysine residues can exhibit varying degrees of methylation (mono-, di-, or tri-methylation), which can result in different biological effects.[33]

For instance, tri-methylation of histone H3 at lysine 4 (H3K4me3) is typically associated with active genes, whereas methylation at H3K9 and H3K27 is linked to gene repression. Research on the role of histone methylation in COPD remains limited. Significant association between the levels of H3K4me3 and increasing mRNA levels of Defensin Beta 1 (DEFB1), which correlates with the pathological progression of COPD.[34]

Furthermore, exposure to hypoxia, a potential trigger for COPD, led to an upregulation of both mRNA and protein levels of Protein Arginine Methyltransferase 2 (PRMT2) in mouse lung tissue.[35] Overall, histone methylation may play a role in COPD pathogenesis, warranting further investigation into the underlying mechanisms.

Histone Phosphorylation

Increased phosphorylation of p38 mitogen-activated protein kinase (p38 MAPK) in alveolar macrophages is a key driver of inflammatory responses in the lungs. The study by Gaffey et al investigates the presence of phosphorylated p38 MAPK in the lungs of COPD patients. The research reveals that levels of phosphorylated p38 MAPK are significantly elevated in the lung tissue of individuals with COPD compared to healthy controls. This increase is associated with heightened inflammatory responses and may contribute to the pathophysiology of COPD.[36]

This phosphorylation process leads to the production of inflammatory cytokines, especially in smokers with COPD. Cigarette smoke activates kinases that promote inflammatory gene

expression through histone phosphorylation. This histone modification facilitates transcription factor access to pro-inflammatory genes. Targeting kinase activation and histone phosphorylation could present potential therapeutic strategies to mitigate chronic inflammation in smokers with COPD, potentially improving disease management by reducing inflammation and slowing progression.[1–3]

The review by Ahmadi et al focuses on the role of p38 MAPK signaling contributes to key processes in COPD, including inflammation, apoptosis, and tissue remodeling. They highlight the pathway's involvement in exacerbating inflammatory responses and the progression of the disease. Additionally, the review evaluates various p38 MAPK inhibitors currently under investigation, emphasizing their potential to reduce inflammation and improve lung function in COPD patients.[37]

Histone Ubiquitination

The ubiquitin-proteasome system (UPS) plays a vital role in regulating protein degradation, particularly in the context of skeletal muscle dysfunction associated with COPD.[38,39] In COPD, especially among smokers, there is a disruption in the balance between muscle protein synthesis and degradation, leading to the loss of contractile proteins in the diaphragm and skeletal muscles.[39]

Activation of the UPS contributes to this imbalance by accelerating the breakdown of these proteins. The expression of pro-inflammatory cytokines is heightened in COPD, further promoting UPS activity and exacerbating muscle degradation. This increased UPS activity, particularly in degrading critical contractile proteins like myosin, significantly contributes to respiratory muscle weakness in COPD patients.[40]

Specifically, smoking upregulates Ubiquitin-specific proteases-19 (USP-19), a deubiquitinating enzyme, through the activation of p38 and extracellular-signal-regulated kinase (ERK)/MAPK pathways. This leads to skeletal muscle atrophy and a significant loss of myosin in the diaphragm, weakening respiratory function in COPD patients. Moreover, given the role of UPS in this process, it presents a potential therapeutic target for interventions aimed at preventing muscle atrophy and preserving muscle function in individuals with COPD.[38]

Noncoding RNA

The study by Ren et al explores the role of noncoding RNAs (ncRNAs) in the pathogenesis and potential treatment of COPD. NcRNAs, including microRNAs (miRNAs) and long noncoding RNAs (lncRNAs), are shown to regulate key cellular processes such as inflammation, apoptosis, and oxidative stress, all of which contribute to COPD progression.[21]

miR-145 exerts a suppressive effect on the release of pro-inflammatory cytokines from airway smooth muscle cells in COPD patients by targeting SMAD Family Member 3 (SMAD3), a key downstream effector in the transforming growth factor

(TGF)-β signaling cascade.[41] By modulating ncRNA activity, it may be possible to develop new therapies aimed at slowing disease progression and improving patient outcomes.[21]

The abnormal expression of long noncoding RNAs (lncRNAs) has been shown to play a role in various diseases, such as COPD. LncRNA NNT-AS1 (NNT-AS1) was up-regulated in CSE-treated 16HBE cells, and its knockdown reversed CSE-induced effects on cell proliferation, apoptosis, inflammation, and airway remodeling, revealing its role in smoking-induced COPD through the miR-582-5p/FBXO11 pathway.[42]

Low expression levels of MCM3AP-AS1 are linked to an increased likelihood of COPD in smokers. COPD development involves airway remodeling, where abnormal proliferation of human bronchial smooth muscle cells (HBSMCs) plays a key role. The study found that MCM3AP-AS1 negatively regulates HBSMC proliferation, indicating its potential as a therapeutic target for COPD.[43] lncRNA COPDA1 enhanced the expression of MS4A1, leading to increased store-operated calcium entry in HBSMCs, which in turn stimulated the proliferation of smooth muscle cells and contributed to airway remodeling.[44]

EPIGENETIC THERAPEUTIC APPROACH OF COPD

Current and emerging therapeutic strategies aim to target epigenetic modifications in COPD. These approaches include agents that reverse or modulate epigenetic changes to mitigate inflammation and disease progression. A combined therapeutic approach utilizing DNMT inhibitors along with anti-inflammatory medications holds significant potential in the treatment of COPD. This strategy is promising because DNMT inhibitors target abnormal DNA methylation patterns, which are linked to inflammation and disease progression in COPD.[21]

By restoring normal gene expression, these inhibitors could reduce the chronic inflammatory response. When used alongside anti-inflammatory drugs, which directly suppress the inflammation, the combination could offer a more comprehensive treatment by addressing both the underlying epigenetic changes and the ongoing inflammatory processes, potentially slowing disease progression and improving patient outcomes.[21]

Diet and environmental factors influence epigenetic mechanisms involved in the pathogenesis of COPD, with nutrients playing a key role in regulating these mechanisms through natural phytochemicals that target signaling pathways in chronic respiratory diseases. Nutritional epigenomics (nutrigenomics) explores how nutrients affect health by modifying gene expression through epigenetic changes, such as DNA methylation and histone modifications, via 1-carbon metabolism.[45,46]

Antioxidants, vitamins, fiber, and dietary patterns have been shown to influence lung health and COPD progression by regulating inflammation,

oxidative stress, and carbon dioxide/oxygen balance. Antioxidant-rich foods, particularly fruits, are positively associated with improved lung function and reduced COPD-related respiratory symptoms and mortality.[47] Natural antioxidants like polyphenols, flavonoids, curcumin, resveratrol, green tea catechins, quercetin, and others show potential in preventing and treating COPD.[45]

A healthy dietary pattern, characterized by a high intake of fruits, vegetables, fish, and whole grains, is associated with a lower risk of COPD. In contrast, a Western diet high in cured and processed meats, red meat, preserved foods, and refined carbohydrates is linked to an increased risk of COPD and respiratory symptoms like coughing with phlegm. The Mediterranean diet, on the other hand, is associated with better lung function, improved spirometric parameters, and a lower prevalence of COPD.[45]

Curcumin, a compound found in turmeric (Curcuma longa), is known for its broad therapeutic effects and protective properties in various diseases. Studies have shown that curcumin can reduce proinflammatory cytokines like IL-1β, IL-6, IL-8, and TNF-α and has antioxidant effects.[48]

In a rat model of COPD induced by cigarette smoke, curcumin was found to block the mRNA expression of proinflammatory molecules (IL-8, MCP-1, MIP-2α) and modulate HDAC2 expression, which plays a role in inflammation. Cigarette smoke reduced HDAC2 expression and altered histone modifications, but curcumin reversed these changes. This suggests that curcumin can reduce inflammation and potentially restore corticosteroid resistance in COPD by modulating HDAC2 and histone modification.[48]

Quercetin, a flavonoid with anti-inflammatory and antioxidant properties, has shown promise in enhancing epithelial regeneration in COPD.[49] It negatively regulates matrix metalloproteinase (MMP) expression, which is crucial for extracellular matrix degradation and tissue damage in COPD. In vitro studies reveal that quercetin promotes the proliferation and differentiation of airway basal cells, aiding epithelial restoration. Its beneficial effects are linked to the modulation of HDAC activity, which influences MMP expression and improves disease outcomes.[50]

In an elastase/LPS mouse model, quercetin prevents COPD progression by downregulating MMPs through HDAC modulation, impacting signaling pathways related to cell proliferation and differentiation. By enhancing the expression of growth factors and cytokines essential for repair, quercetin emerges as a potential therapeutic strategy for COPD, contributing to better symptom management and lung function improvement.[50]

Theophylline restores HDAC activity and enhances steroid responsiveness in COPD macrophages. Theophylline, at low doses, was shown to increase HDAC activity in COPD macrophages, thereby

improving their responsiveness to corticosteroids. This suggests that theophylline may help overcome steroid resistance in COPD patients, potentially enhancing the efficacy of steroid treatments and reducing inflammation more effectively.[51]

This suggests that theophylline could be a valuable adjunctive treatment for improving steroid sensitivity and managing inflammation in COPD. The systematic review and meta-analysis by Shuai et al evaluated the effects of adding low-dose theophylline to inhaled corticosteroid (ICS) therapy in patients with COPD. The study assessed clinical outcomes such as lung function, exacerbation frequency, and quality of life. The results indicate that low-dose theophylline combined with ICS offers modest improvements in lung function and symptom control compared to ICS alone.[52]

However, the clinical significance of these benefits is limited, and theophylline's potential side effects, including its narrow therapeutic range, warrant cautious use. The study highlights the need for further research on the optimal use of this combination therapy in COPD management.[52]

CONCLUSION

Understanding the epigenetic landscape of COPD reveals critical insights into novel therapeutic avenues for this complex disease. DNA methylation and histone modifications significantly influence key cellular processes, including inflammation, cell cycle regulation, and apoptosis, which are central to COPD progression. Despite growing recognition of the role of epigenetic alterations in COPD, the underlying molecular mechanisms remain poorly defined. Therefore, advancing research in this area is crucial for unraveling these intricate pathways and developing targeted interventions that can reverse or mitigate epigenetic changes. Such therapeutic strategies hold the potential to significantly improve disease management and patient outcomes, making this an urgent priority in the future of COPD treatment.

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