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An Epigenetic Insight into Chronic Obstructive Pulmonary Disease: From DNA Methylation Mechanisms to Therapeutic Strategies

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Abstract

Chronic Obstructive Pulmonary Disease (COPD) represented a complex respiratory disorder influenced by a combination of genetic and environmental factors. This review highlighted the pivotal role of DNA methylation in the pathogenesis and progression of Chronic Obstructive Pulmonary Disease. By examining the function of DNA methylation, particularly hypermethylation, the authors identified key targets genes involved in lung maturation, inflammation, and oxidative stress, which contributed to the worsening of Chronic Obstructive Pulmonary Disease. The review also explored the significance of DNA methylation in the biomarker field, environmental factors, and treatment methods. Through a com- prehensive analysis, the authors elucidated the impact of hypermethylation on genes such as Interleukin-1 Beta, which was associated with inflammatory processes in Chronic Obstructive Pulmonary Disease lungs. Furthermore, the review discussed emerging therapeutic procedures, including epigenome editing through CRISPR technology and DNA methyltransferase inhibitors, demonstrating their potential in personalized Chronic Obstructive Pulmonary Disease management. The authors proposed that the integration of these novel approaches with conventional pharmacological interventions might offer a more comprehensive treatment plan tailored to each patient's specific molecular characteristics.

Keywords: COPD, Epigenetic, CRISPR, Methylation

1. Introduction

The relationship between genetic predisposition and environmental factors plays a significant role in shaping the intense landscape of human health. Within this, epigenetic mechanisms, particularly DNA methylation, have been pivotal in influencing gene ex- pression without altering the original underlying genetic code (Cheng,2016). Further, environmental factors have been proven to affect pathology to a great extent. For example, chemical pollutants, such as heavy metals and industrial toxins, can contribute to cellular damage and dysfunction, leading to conditions ranging from respiratory illness to neurological disorders (Bailey et al., 2012). Moreover, biological agents present in the environment, such as pathogens and allergens, can trigger immune responses and bring about infectious diseases or allergic reactions (Barnes, 1970; Cheng, 2016). On the other hand, socioeconomic and lifestyle factors, including access to healthcare, socioeconomic status, diet, and physical activity, also shape disease patterns and outcomes within populations (Clifford et al., 2018).

In the context of respiratory health, unraveling the epigenetic organization of genes in organs such as the lungs and bronchi are necessary for understanding the complexities of physiological processes and the pathogenesis of respiratory diseases (Dan-Dan, W. 2017) (David et al.,2015). Among these, COPD is a multifaceted condition characterized by airflow limitation and persistent respiratory symptoms(Donald et al., 2009). Moreover, COPD holds an immense significance within healthcare and society. As the second leading

Vol. 2024 (10) 388 – 402
ISSN 2688-3651 [online]

cause of death in the world, the illness affects a wide range of people and accounts for a considerable portion of global disability-adjusted life years (DALYs) lost (Barnes & Celli, 2009). Not only does COPD affect patient health, but it also puts a substantial burden on the healthcare system through healthcare utilization, lost productivity, and premature mortality (Bailey et al., 2012; Barnes, 1970). Furthermore, COPD is often associated with other chronic conditions, which exacerbates the complexity of patient management and places an additional strain on the healthcare system. Asa result, this paper delved into the effects of epigenetic modifications on the molecular landscape associated with COPD, with a specific focus on DNA hypermethylation.

This paper aimed to investigate the role of DNA methylation and other epigenetic modifications in the development and progression of COPD. Firstly, the current under- standing of DNA methylation, in relation to its parentage of epigenetic modifications, was examined. Next, COPD was explored, including its definition and current state within the medical field. Following this, the overall effect of various epigenetic modifications on COPD was assessed, with a particular focus on DNA hypermethylation. Due to the importance of DNA hypermethylation in the epigenetic mechanisms that contribute to COPD, this specific modification received significant attention. DNA hypermethylation is extremely significant because of its connection to regulating numerous cellular processes, including embryonic development, genomic imprinting, X-chromosome inactivation, and tissue-specific gene expression (Castaldi et al., 2009). Disorders of DNA methylation have been implicated in a wide array of diseases, including cancer, neurological disorders, and autoimmune conditions, underscoring its seriousness in health and disease (Cheng, 2016). Furthermore, environmental factors, lifestyle choices, and aging can influence DNA methylation patterns, highlighting its susceptibility to external stimuli which, in turn, can lead to various illnesses, including COPD (Clifford et al., 2018). Current therapeutic solutions for this issue were also investigated, with suggestions for new ways to relieve individuals from this disease. Additionally, the paper explored the environmental and lifestyle factors that may influence DNA methylation in the context of COPD. By understanding how factors such as smoking, air pollution, and occupational exposures affect DNA methylation patterns, the complex interplay between epigenetic modifications and environmental triggers in COPD development was highlighted (Donald, 2009).

By understanding these concepts in this review, individuals, healthcare professionals, and society as a whole can understand the complexity of COPD. Since COPD represents a significant public health burden globally by contributing to morbidity, mortality, and healthcare costs, it is incredibly important to recognize the various causes of the disease properly (Golpon et al., 2001). Currently the healthcare system uses more traditional approaches to COPD management, 110 which often focus on symptom relief and disease stabilization; however these therapies may not address underlying molecular mechanisms (He et al., 2020; Tønnesen, 2013). By reviewing the epigenetic modifications associated with COPD, such as histone modifications, non-coding RNA, and especially DNA methylation, researchers can unwind novel insights into disease pathogenesis and identify new target for intervention (Vogelmeier et al., 2020; Sundar et al., 2024; Thomas, 2024). Moreover, understanding the role of epigenetics in COPD reveals the importance of preventative measures, such as smoking cessation and environmental regulations, in reducing disease risk and progression (Miravitlles & Ribera, 2017).

2. What is COPD?

According to the Centers for Disease Control and Prevention (CDC), COPD is the sixth largest cause of death in the United States, showing just how many people the disease affects (The Lancet, 2024a; Kristina et al., 2012)—an ongoing, irreversible restriction in airflow marks COPD. A collection of progressive respiratory illnesses de- fined by persistent airflow limitation is included in the clinical definition of this dis- ease (López-Campos et al., 2024). As shown in Figure 1, this restriction is typically linked to long-term lung parenchymal and airway inflammation. As the second leading cause of death worldwide, COPD has a major influence on public health (Sean et al., 2015; Sundar et al., 2024; Wang et al., 2020). The main cause of this illness is extended exposure to irritant gases or particulate matter, which is most frequently inhaled through cigarette smoke. Besides smoking, COPD also develops as a result of other variables such as genetic predispositions, occupational exposures, and air pollution (Figure 1). COPD includes two primary forms: emphysema, which is defined by damage to the lung's air sacs that reduce their elasticity, and chronic bronchitis, which is characterized by inflammation

Vol. 2024 (10) 388 – 402
ISSN 2688-3651 [online]

and narrowing of the bronchial tubes (Sidhaye et al., 2018).

The main signs of COPD are chronic cough, increased mucus production, wheezing, and shortness of breath (Miravitlles & Ribera, 2017). People frequently have exacerbations as the condition worsens, which are characterized by an abrupt worsening of symptoms and a subsequent loss of lung function (Linling et al., 2016). In addition to having a significant negative impact on respiratory health, COPD has systemic effects that lead to a number of comorbidities such as coronary artery disease, heart failure, and hypertension as well as an increased risk of pneumonia and bronchitis due to compromised lung function and impaired immune responses (Moon et al., 2021).

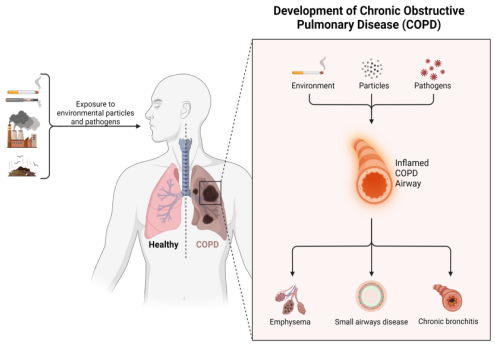

Figure 1: The Development of COPD

In the case of COPD, pulmonary function tests are used to identify airflow limitation in patients, and bronchodilator drugs, inhaled corticosteroids, smoking cessation, and pulmonary rehabilitation are commonly used in the treatment of the condition (Robertson & Jones, 2000). COPD persists despite continuous attempts to reduce risk factors and improve treatment approaches.

COPD is still a major global health concern that requires extensive research and treatments to enhance patient outcomes and quality of life. A comprehensive of the patient's clinical symptoms, medical history, and objective lung function assessments are necessary for diagnosing COPD. The assessment of pulmonary function using spirometry, a popular and accurate test that assesses a number of parameters, including Forced Vital Capacity (FVC), is an essential part of the diagnosis process for COPD. One important diagnostic technique is spirometry, which measures the volume and velocity of air that can be breathed and expelled (Lapperre et al., 2006). Forced Vital Capacity, a crucial metric derived from spirometry denotes the air an individual can compel themselves to expel following a profound breath (Yi et al., 2018). Reduced Forced Vital Capacity is a characteristic of airflow limitation in COPD, mostly due to the obstructive component of the disease. The blockage causes the lungs to take longer to empty during exhale, which lowers the forced vital capacity (Jill et al., 2015; Lin- ling et al., 2016; Sean et al., 2015). The ability to differentiate between restrictive and obstructive lung disorders can be achieved using the Forced Vital Capacity measurement. Another important spirometric parameter, forced expiratory volume in one second (FEV1), decreases COPD and fall in forced vital capacity(Sean et al., 2015). It is common practice to utilize the FEV1/FVC ratio to determine whether airflow re- striction exists. The defining characteristic of COPD24 is persistent airflow limitation, which is indicated by a lower FEV1/FVC ratio (< 70%) (Tønnesen et al., 2013).

In addition to spirometry, other diagnostic methods, including chest X-rays or CT scans, may be used to evaluate lung anatomy and rule out other possible causes of illness (Lapperre et al., 2006). Blood gas analysis can also give information on blood oxygen and carbon dioxide levels, which can help determine how severe a patient's respiratory impairment is if they have COPD(Sundar et al., 2024).

On the other hand, the immune system plays a critical role in COPD pathogenesis, contributing to chronic inflammation, tissue damage, and lung remodeling(The Lancet, 2024b). In response to inhaled irritants such as cigarette smoke and environmental pollutants, immune cells in the lungs, including macrophages, neutrophils, and T lymphocytes, become activated, releasing pro-inflammatory mediators and creating a state of chronic inflammation(Singh, 2017).

Conversely, one emerging area of research in COPD pathophysiology is the role of cellular senescence. Senescent cells have entered a state of irreversible growth in response to various stressors, including DNA damage, oxidative stress, and inflammation (Castaldi et al., 2009). While senescent cells serve as a protective mechanism to pre- vent the proliferation of damaged cells, recent studies suggest that senescent cells play a detrimental role in COPD (He et al., 2020). Senescent cells secrete a complex array of pro-inflammatory cytokines, chemokines, and extracellular matrix-degrading enzymes, collectively known as the senescence-associated secretory phenotype (SASP) (Marianne et al., 2007). This SASP can cause chronic inflammation,

Vol. 2024 (10) 388 – 402
ISSN 2688-3651 [online]

promote tissue fibrosis, and impair tissue repair mechanisms within the lungs, contributing to the pathogenesis of COPD (Marianne et al., 2007; Jonathan et al., 2020).

Moving on, studies have shown that many epigenetic modifications have been observed as one of the causes of COPD, and DNA methylation in particular have shown to deviate from normal methyl levels in COPD patients.

3. The Intricacies of DNA Methylation

3.1 Understanding DNA Methylation

DNA methylation, an important epigenetic modification, involves adding of methyl groups (-CH3) to cytosine residues, particularly in CpG dinucleotides (Marta et al., 2010). This modification is done by a family of enzymes known as DNA methyltransferases (DNMTs), with DNMT1, DNMT3a, and DNMT3b being the primary ones and this process usually occurs in regions rich in CpG islands, often located in gene promoter regions (Moon et al., 2021; Scharm et al., 2022; Sundar et al., 2024). Methylation at these sites acts as a regulatory switch, influencing gene expression patterns by either promoting transcriptional repression or regulating gene activation (Scharm et al., 2022). In the context of DNA hypermethylation, which is the excessive addition of methyl groups, the gene promoter regions become densely methylated, leading to a suppressed transcriptional state (Sundar et al., 2024) (Figure 2). This can result in the silencing of crucial genes associated with a multitude of cellular processes. On the other hand, hypomethylation, or the removal of methyl groups, is linked to gene activation, allowing for the expression of specific genes (Sundar et al., 2024; Marianne et al., 2007).

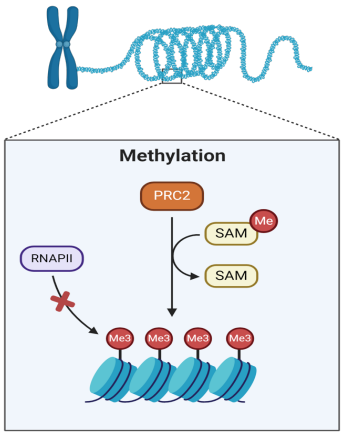

Figure 2: DNA Hypermethylation occuring within the chromosome and the inhibition of mRNA

The figure above shows the formation of DNA hypermethylation with the use of PRC2 and SAM. Polycomb Repressive Complex 2 (PRC2) is a multi-protein complex that is found within eukaryotic cells, and play a centra role with DNA methylation. The core com- ponents of PRC2 include EZH2 (Enhancer of Zeste Homolog 2), which is the catalytic subunit responsible for methyltransferase activity, along with other proteins such as EED (Embryonic Ectoderm Development) and SUZ12 (Suppressor of Zeste 12). These proteins work together to recognize specific chromatin regions and regulate the addition of methyl groups to histones. On the other hand, S-adenosylmethionine (SAM) isa key molecule involved in methylation reactions, serving as the primary methyl group donor. In the case of this figure, the amount of methyl groups that SAM is adding to the chromosome is to many, causing RNAPII, which is used for mRNA transcribing, is blocked. Therefore, silencing that gene.

3.2 DNA Methylation's role in COPD

Within the respiratory system, the DNA methylation process plays a nuanced role in the regulation of genes crucial for lung development, immune response, and airway main- tenance (Rauluseviciute et al., 2020). Alterations in this epigenetic landscape, whether through hypermethylation or hypomethylation, can disrupt the delicate equilibrium of gene expression, potentially contributing to the onset and progression of respiratory diseases. Understanding these molecular complexities is essential for unwinding the connection between epigenetic modifications and respiratory health (Scholthof, 2006; Shaikh & Bhandary, 1970; Thomas, 2024).

Specifically looking at DNA methylation, studies have shown that there is deviant DNA methylation patterns in COPD patients, particularly in genes involved in inflam- mation, oxidative stress, and tissue remodeling pathways (Linling et al., 2016). For example, the DNA hypermethylation of genes associated with antioxidant defenses, such as *glutathione S-transferase* (*GSTP1*), can impair their expression, leading to in- creased oxidative stress and inflammation in the lungs (Petty, 2024; Rauluseviciute et al., 2020). Similarly,

Vol. 2024 (10) 388 – 402
ISSN 2688-3651 [online]

hypomethylation of pro-inflammatory genes, such as *interleukin-8* (*IL-8*), may aggravate airway inflammation and mucus production that is characteristic for COPD(Branson, 2018). Further, environmental variables, such as cigarette smoke and air pollution, can induce DNA methylation changes in susceptible individuals, fur- ther creating a risk of COPD (Golpon et al., 2001).

4. Epigenetics and COPD

Genetic alterations can have a substantial effect on the respiratory system and may be involved in the onset of COPD. Genetic predispositions can increase susceptibility to COPD, even if environmental factors like air pollution and tobacco smoke are the main causes of the disease. COPD-related genetic alterations frequently affect genes responsible for preserving lung integrity, controlling inflammation, and fending off oxidative stress (Michael et al., 2012).

One notable genetic factor is Alpha-1 Antitrypsin (AAT) deficiency, a genetic disorder brought on by mutations in the SERPINA1 gene. The protein AAT is essential for preventing lung damage by blocking enzymes that degrade lung tissue (Jill et al., 2015). As seen in Figure 3, mutations in SERPINA1 can result in unchecked enzyme activity, accelerating the deterioration of lung tissue and raising the risk of COPD, especially in younger individuals. In addition to AAT deficiency, genetic differences in other path- ways, such as those pertaining to immunological regulation and inflammatory responses, can influence susceptibility to COPD. For instance, variations in immune system-related genes, such as tumor necrosis factor-alpha (TNF-alpha), have been connected to heightened airway inflammation, aggravating the symptoms of COPD (Miravitlles & Ribera, 2017).

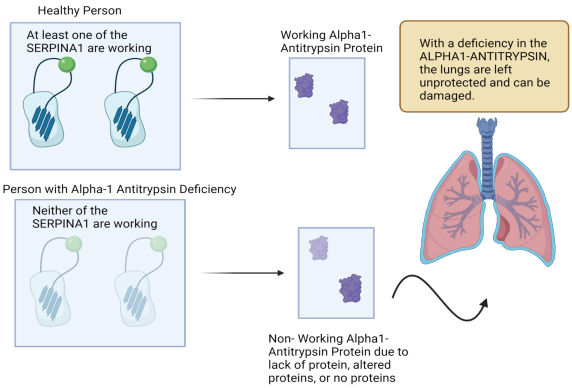

Figure 3: The Effects of Alpha-1 Antitrypsin Deficiency on the Lungs

Understanding the genetic foundations of COPD is crucial for identifying at-risk individuals and creating individualized treatment plans. Genetic testing and ongoing research efforts are vital for revealing the complex relationships between genetic mutations, respiratory system function, and the pathogenesis of COPD. Variations in genes linked to lung development, like surfactant proteins, and mucin synthesis, which influences the viscosity and clearance of airway mucus, have also been implicated (Jonathan et al., 2020). These differences may interfere with regular breathing patterns, making a person more susceptible to environmental stressors and accelerating the onset of COPD. Genetic changes that affect how the body reacts to oxidative stress are also important. The lungs' capacity to combat dangerous free radicals can be weakened by mutations in genes related to antioxidant defenses, such as glutathione S-transferase (GST) genes. This can lead to tissue damage and persistent inflammation characteristic of COPD. New susceptibility genes and pathways are being discovered through ongoing research into the genetic basis of COPD. A deeper comprehension of each per- son's unique illness risk and progression is made possible by the combination of genetic data and environmental risk factors (Ranu et al., 2011; Marianne et al., 2007; Eeden & Hogg, 2019).

Recent studies indicate that histone modifications—alterations to the proteins that envelop DNA-may also play a role in the etiology of COPD. Histone modifications are essential in the control of gene expression. Changes in acetylation, methylation, and phosphorylation patterns are the main histone modifications linked to COPD. These modifications contribute to the deregulation of important genes related to inflammation, tissue remodeling, and oxidative stress (Kotlyarov, 2022).

Abnormal histone acetylation in COPD affects the accessibility of genes related to the inflammatory response. Increased histone acetylation can lead to higher expression of pro-inflammatory mediators, sustaining the persistent inflammation characteristic of COPD. Conversely, anti-inflammatory genes have been linked to

Vol. 2024 (10) 388 – 402
ISSN 2688-3651 [online]

histone deacetylation, leading to gene silencing and exacerbating the inflammatory cascade in the lungs. Histone methylation patterns are also crucial in COPD pathophysiology (Decramer & Cooper, 2010). Altered histone methylation in genes involved in tissue remodeling and repair can compromise natural repair processes in the lungs, contributing to the progressive loss of respiratory function in COPD patients. Histone phosphorylation, a dynamic alteration linked to various cellular functions, has been connected to oxidative stress in COPD. The activation of genes involved in antioxidant defense mechanisms may be influenced by histone phosphorylation, and deregulation of this process may lead to increased vulnerability to oxidative damage, a critical element in COPD progression (Scharm et al., 2022).

Long non-coding RNAs (lncRNAs) have emerged as significant players in epige- netic regulation and disease. Unlike protein-coding RNAs, lncRNAs do not function as templates for protein production but are essential for controlling various biological functions, such as gene expression, chromatin remodeling, and epigenetic changes. Several lncRNAs have been linked to the onset and progression of COPD (Thomas, 2024; Tønnesen, 2013). For instance, elevated levels of the lncRNA H19 have been found in the lungs of COPD patients, with deregulation of this gene linked to higher levels of inflammation and oxidative stress. MALAT1 (Metastasis-Associated Lung Adenocarcinoma Transcript 1) is another lncRNA connected to the severity and advancement of COPD. MALAT1 contributes to the tissue remodeling observed in COPD by influencing the migration and proliferation of lung fibroblasts (Clifford et al., 2018).

5. DNA Hypermethylation is Prominent in COPD

One important epigenetic process that has been linked to the development and increased risk of COPD is DNA methylation, specifically hypermethylation (Miravitlles et al., 2017; Rappaport et al., 2024). Gene expression patterns can be changed as a result of hypermethylation, which is the addition of methyl groups to particular cytosine residues inside the DNA molecule (Sundar et al., 2024). Hypermethylation has been linked to changes in important genes and pathways related to inflammation, tissue repair, and respiratory function in the context of COPD (Vogelmeier et al., 2020).

Hypermethylation has the potential to increase the risk of COPD by inhibiting genes linked to lung development and upkeep (Scholthof, 2006) (Figure 4). For example, the inability of the respiratory system to heal from harm brought on by things like cigarette smoke or environmental contaminants may be hampered by the hypermethylation of genes involved in lung tissue regeneration and repair (The Lancet, 2024a). This im- paired repair mechanism may be a factor in the COPD-associated gradual reduction in lung function. As shown in Figure 4, genes linked to inflammatory processes have been found to be hypermethylated. One of the main characteristics of COPD is chronic inflammation, which may be made worse by hypermethylation-induced inhibition of anti-inflammatory genes or activation of pro-inflammatory genes. Prolonged inflammation has the potential to cause tissue damage, reshape airways, and cause the typical airflow restriction linked to COPD (UpToDate, 2024).

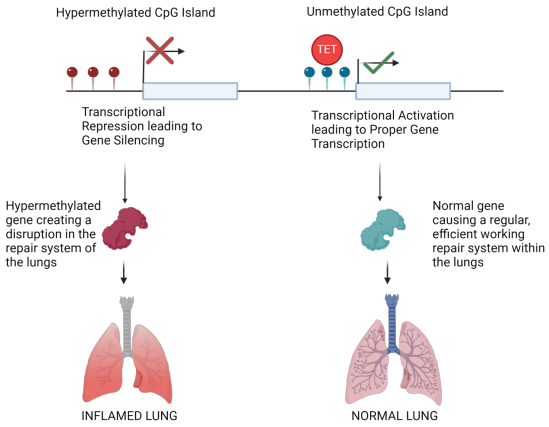

Figure 4: Hypermethylation's effect on the lungs

Moreover, oxidative stress is a major component in the pathophysiology of COPD and greater vulnerability to it may result from hypermethylation in genes linked to antioxidant defense mechanisms (Sin et al., 2006). Hypermethylation-induced reduced antioxidant capacity can lead to an imbalance between the generation and neutralization of reactive oxygen species, which can cause oxidative damage and exacerbate lung inflammation (Kristina et al., 2012).

Therefore, a major factor contributing to the increased risk of developing COPD is hypermethylation in particular genes linked to lung growth, inflammation, and oxidative stress (Kristina et al., 2012). Comprehending

Vol. 2024 (10) 388 – 402
ISSN 2688-3651 [online]

the epigenetic alterations implicated in the etiology of COPD, such as hypermethylation, provides opportunities for focused therapeutic approaches that target DNA methylation patterns to slow down the dis- ease's course and enhance patient outcomes (Laia et al., 2010).

However, research on the familial clustering of COPD has found potentially heritable DNA methylation patterns (Du et al., 2019). Understanding the genetic foundation of COPD risk can be gained by examining the epigenetic changes in certain genes linked to vulnerability to the disease (Miravitlles & Ribera, 2017; Rappaport, 2024). A possible hereditary component of epigenetic regulation in COPD has been highlighted by familial studies that have revealed certain genomic areas where DNA methylation pat- terns may be altered in individuals with a family history of the disease (López-Campos et al., 2024). Furthermore, genetic variations linked to COPD risk have been found using genome-wide association studies (GWAS), and some of these variants have been connected to alterations in DNA methylation (Vogelmeier et al., 2020). GWAS is a tool that can be used by scanning the genomes of thousands of individuals to identify genetic variations associated with particular traits or diseases across the entire genome. GWAS can pinpoint single nucleotide polymorphisms (SNPs) or other genetic mark- ers statistically linked to the trait or condition of interest (Eeden & Hogg, 2019). The results from the GWAS imply that hereditary variables may impact the epigenetic environment, resulting in modified DNA methylation patterns that may raise the chance of getting COPD. DNA methylation is a crucial mediator in the dynamic process of gene expression regulation that underlies the interplay between genetic and epigenetic vari- ables (Shaikh et al., 1970). Comprehending the hereditary susceptibility to COPD by DNA methylation holds wider consequences for customized healthcare and prophylactic measures. The *Interleukin-1 Beta IL1B* gene is one that is impacted by DNA hypermethylation in the context of COPD (Easter et al., 2020). The *IL1B* gene is related to a pro-inflammatory cytokine involved in the immune response. *IL1B* is critical in mediating inflammation and immune reactions (Kristina et al., 2012)(Laia et al., 2010). The pathophysiology of COPD has been linked to deregulation of *IL1B* expression, which is essential to the inflammatory response in the lungs (López-Campos et al., 2024). People with COPD have been shown to have DNA hypermethylation of the *IL1B* gene promoter region, which lowers gene expression levels. This abnormal methylation pattern is a contributing factor to COPD's chronic inflammation and tissue destruction (Rauluseviciute et al., 2020). Prolonged exposure to cigarette smoke and other environmental contaminants causes lung tissue and airways to remain inflamed in people with COPD (Scholthof et al., 2006). The expression of the *IL1B* gene is silenced by hypermethylation of its promoter region, which lowers interleukin-1 beta levels (Sean et al., 2015). In individuals with COPD, this dysregulation exacerbates the inflammatory response and accelerates the course of their disease by upsetting the equilibrium of inflammatory mediators in the lungs (Jill et al., 2015). Additionally, tissue repair mechanisms may be compromised and the structural alterations in the alveoli and airways associated with COPD may be aggravated by the downregulation of *IL1B* brought on by DNA hyper- methylation (Yi et al., 2018). Matrix metalloproteinases (MMPs) and other proteases that aid in tissue remodeling and healing are regulated by *IL1B*. Decreased expression of *IL1B* hinders the lungs' capacity to heal from inflammation-induced damage, which causes the condition of COPD patients to worsen in terms of airflow restriction and respiratory symptoms (Singh, 2017). Finding people with particular DNA methylation profiles linked to an increased risk of COPD may make it possible to implement targeted interventions, such as early lifestyle changes, monitoring, and possibly even the creation of preventive treatments (Ranu et al., 2011). It's crucial to remember that COPD is a multifaceted illness, and that the intricate interactions between genetic and environmental factors that contribute to its development are unlikely to be entirely explained by genetic predisposition alone (Thomas, 2024).

6. Therapeutic Solutions

In the context of COPD, therapeutic interventions that target DNA methylation offer a promising frontier in the search for novel treatment approaches (Scholthof, 2006). A major factor in the pathophysiology of COPD is the disruption of DNA methylation patterns, which impacts important genes related to oxidative stress, inflammation, and tissue repair. Using cutting-edge technology, such as CRISPR-Cas9 and other recently developed medical technologies, presents previously unheard-of possibilities for accuracy when treating the epigenetic changes linked to COPD (Thomas, 2024).

Vol. 2024 (10) 388 – 402
ISSN 2688-3651 [online]

6.1 The Current State of COPD Treatment

Currently, the medical community treats COPD using a multimodal strategy that aims to manage symptoms, improve lung function, and improve the overall quality of life for those who are afflicted (Miravitlles & Ribera, 2017; Robertson & Jones, 2000). Bronchodilators are frequently recommended to treat airflow restriction and lessen symptoms like dyspnea. These include anticholinergics and both short- and long-acting beta-agonists. For patients with more severe COPD or those who experience exacerbations often, inhaled corticosteroids may be added (Wiley Online Library, 2024). These pharmaceutical therapies address the main physiological issues related to COPD by aiding in bronchodilation and inflammation control (Sin et al., 2006). Programs for pulmonary rehabilitation, which place a strong emphasis on exercise instruction, education, and nutritional support, are essential parts of managing COPD (Petty, 2024). These programs aim to enhance exercise tolerance, lower dyspnea, and equip patients with self management techniques. Quitting smoking is one of the most important lifestyle changes you can make to decrease the progression of your disease. The most effective management for COPD patients is still quitting smoking, which dramatically lowers the rate of lung function decrease and improves overall health outcomes (Lapperre et al., 2006).

6.2 Current Treatment of COPD Has Unanswered Issues

Even with advancements in COPD treatment, patients are still affected by unfavorable characteristics and enduring obstacles (Easter et al., 2020). One major worry is that COPD is still an incurable, progressive illness, and the majority of existing medications are aimed at managing symptoms rather than curing the illness. Due to this restriction, patients frequently have to contend with the disease's cumulative effects on their respiratory system and general health for the rest of their lives (Decramer & Cooper, 2010; Donald et al., 2009). Another drawback is the possibility of side effects from prolonged pharmaceutical use, especially inhaled corticosteroids. Adverse effects such as oral thrush, a higher risk of pneumonia, and systemic symptoms could add to the difficulties that patients already face when adjusting to the complicated nature of COPD (Laia et al., 2010). Moreover, certain individuals may not respond optimistically to conventional pharmaceutical interventions, underscoring the necessity for more individualized and efficacious therapeutic alternatives (Miravitlles & Ribera, 2017). Furthermore, it is impossible to ignore the socioeconomic cost of treating COPD (Ranu et al., 2011). Patients may experience financial difficulties due to the expenses of prescription drugs, pulmonary rehabilitation programs, and hospital stays, which can put a burden on healthcare systems. The detrimental effects of existing COPD treatments are highlighted by their influence on everyday functioning and quality of life, as well as the psychological cost of having a chronic and progressive condition (Sidhaye et al., 2018). Addressing these issues and creating more focused and effective interventions will be essential as medical research develops in order to improve results and lessen COPD patients' burdens.

6.3 A Novel Remedy: CRISPR

Because of this, the treatment of COPD may be entirely changed by cutting-edge medical technologies like CRISPR-Cas9 (Tønnesen, 2013). Clustered Regularly Interspaced Short Palindromic Repeats, or CRISPR, is a novel genome editing technique that has attracted a lot of interest due to its potential use in treating a variety of genetic dis- eases, including those linked to abnormal DNA methylation patterns like COPD. The two primary parts of the CRISPR system—a Cas protein, also known as Cas9—and guide RNA (gRNA) are taken from a bacterial immune system. The Cas protein functions is a molecular scissor and can cut DNA at the specified site. In contrast, the gRNA targets a particular DNA sequence that is complementary to its sequence (Marta et al., 2010).

CRISPR-based epigenome editing techniques usually entail altering the DNA methylation patterns at particular genomic loci linked to the pathophysiology of the illness in order to address DNA hypermethylation in COPD (Lapperre et al., 2006). The first step in this procedure is to create and synthesize a complementary gRNA to the tar- get hypermethylated genome region. After that, the gRNA and Cas protein combine to form a ribonucleoprotein (RNP) complex, which is frequently transported into the target cells via lipid

Vol. 2024 (10) 388 – 402
ISSN 2688-3651 [online]

nanoparticles or viral vectors (Thomas et al., 2024). As shown in Figure 5, The CRISPR RNP complex searches the genomic DNA for sequences that match the gRNA once it has entered the cell (Sidhaye et al., 2018; Sundar et al., 2024). The Cas protein causes a double-stranded break in the DNA when it comes into contact with the targeted hypermethylated area. The cell's DNA repair machinery is activated by this break, and through processes including base excision repair and homology-based repair, the hypermethylated cytosine residues may be replaced or removed (Moon et al., 2021). CRISPR-based epigenome editing seeks to restore normal gene expression levels and reduce inflammation in COPD patients by altering the DNA methylation patterns at particular loci (Linling et al., 2016).

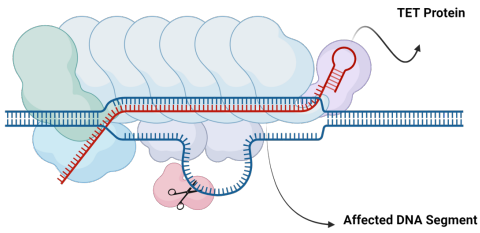

Figure 5. The use of a TET Protein from CRISPR Cas9 to remediate an epigenetically affected DNA Strand

Targeting genes associated with inflammation and tissue remodeling - two major causes of the persistent airway blockage observed in COPD - is one area of focus for CRISPR treatment of COPD(Sin et al., 2006). Through targeted gene modification linked to these mechanisms, CRISPR may be able to reduce or even reverse the inflammatory response and the advancement of COPD (Castaldi et al., 2009). Furthermore, CRISPR might provide a more individualized strategy by enabling the creation of personalized treatments based on each patient's own genetic makeup. Several medical approaches are being researched to modify DNA methylation in addition to CRISPR (Barnes, 1970).

6.4 Other Solutions For COPD Therapy

Zinc finger proteins and transcription activator-like effector nucleases, or TALENs, are examples of epigenome-editing technologies that offer substitute techniques for precise alterations of DNA methylation patterns (Kristina et al., 2012). With the help of these technologies, it is possible to precisely construct enzymes with the ability to add or remove methyl groups at particular genomic loci (Emil et al., 2015). This level of specificity shows potential for use in COPD therapy. Additionally, research is being done on tiny compounds that target DNA methyltransferases (DNMTs), which are the enzymes that add methyl groups to DNA (Marianne et al., 2007). Preclinical research has demonstrated the potential of DNMT inhibitors, including decitabine and azacitidine, to correct abnormal DNA methylation patterns. There is optimism for the development of pharmaceutical therapies that could normalize DNA methylation and change the course of the disease since clinical trials examining the safety and effectiveness of these inhibitors in COPD patients are now underway (David et al., 2015; Decramer & Cooper, 2010; Donald et al., 2009)

6.5 Potential Use of Precision Medicine for COPD

Despite being in its early phases of research, these therapeutic methods highlight the potential of precision medicine in treating COPD (Singh, 2017). However, before these technologies are extensively used in clinical settings, issues including off-target effects and long-term safety concerns need to be resolved (Shaikh & Bhandary, 1970). The in- corporation of these state-of-the-art technologies into the COPD treatment landscape signifies a paradigm shift toward more individualized and focused interventions, with the potential to improve the quality of life and outcomes for those afflicted with this crippling respiratory disease. Apart from genome editing and epigenome modification technologies, current investigations are looking into possibly merging these methods with conventional pharmaceutical interventions (Thomas, 2024; Tønnesen, 2013). Targeted DNA methylation changes and already prescribed COPD drugs, such as bronchodilators and anti-inflammatory medicines, may work together to offer a comprehensive and multimodal therapeutic approach (Yang & Li, 2020). With an eye toward a more comprehensive and successful treatment outcome, this integrated strategy aims to address both the underlying epigenetic changes and the clinical manifestations of COPD (Laia et al., 2010; Lapperre et al., 2006; Miravitlles & Ribera, 2017). A further line of investigation for customized treatment in

Vol. 2024 (10) 388 – 402
ISSN 2688-3651 [online]

COPD is patient categorization based on epigenetic profiling (Thomas, 2024). By identifying distinct DNA methylation pat- terns linked to various COPD phenotypes, medical professionals can customize therapy approaches to the distinct biological attributes of individual patients (UpToDate, 2024). This strategy improves therapeutic precision while also paving the way for a more sophisticated knowledge of the heterogeneity within COPD (Echevarria et al., 2021). This will enable more precise prognostication and tailored therapies that correspond with the unique pathophysiological pathways in each case (Cavaillès et al., 2013).

6.6 A Senolytic Approach

On the other hand, senolytics, are emerging as a promising therapeutic approach in COPD,by specifically targeting senescent cells(Jill et al., 2015). By selectively eliminating senescent cells, senolytics aim to alleviate inflammation, promote tissue repair, and improve lung function in COPD patients. Preclinical studies utilizing various senolytic agents have shown promising results in mitigating lung inflammation, reducing fibrosis, and restoring lung function in animal models of COPD. Moreover, the potential benefits of senolytic therapy extend beyond the lungs, as senescent cell clearance has been as- sociated with improvements in age-related comorbidities commonly observed in COPD patients, such as cardiovascular diseases and osteoporosis (Lapperre et al., 2006; Linling et al., 2016; López-Campos et al., 2024). While further research is needed to under- stand the safety and efficacy of senolytic therapies in COPD, targeting senescent cells holds significant promise as a novel therapeutic strategy for combating the progressive decline in lung function and improving outcomes in COPD patients (Ranu et al., 2011).

6.7 Limitations & Challenges of COPD Treatments

Despite the promising advancements in CRISPR-based epigenome editing, zinc finger proteins, TALENs, DNMT inhibitors, and senolytic therapies, several significant limitations and challenges must be addressed to develop effective treatments for COPD. One of the primary concerns is the potential for off-target effects, particularly with genome-editing technologies like CRISPR. Unintended modifications to the DNA could lead to unpredictable and potentially harmful consequences, such as the activation of oncogenes or disruption of essential genes. Additionally, the long-term safety of these interventions remains uncertain, as it is crucial to understand how these treatments will interact with the complex and dynamic human genome over extended periods (Yi et al., 2018; Zeng et al., 2020).

Achieving precise targeting of hypermethylated regions or senescent cells within the lungs requires advanced delivery systems capable of reaching the affected areas without affecting healthy tissue. Furthermore, the heterogeneity of COPD, characterized by varying phenotypes and molecular profiles among patients, complicates the development of a one-size-fits-all treatment. Personalized approaches based on individual genetic and epigenetic profiles necessitate extensive research and validation, which can be time- consuming and costly (Vogelmeier et al., 2020; Wang et al., 2020).

Environmental and lifestyle factors that contribute to DNA methylation patterns in COPD further complicate treatment development. Factors such as smoking, air pollution, and occupational exposures can continually influence the epigenome, potentially undermining therapeutic efforts (Thomas et al., 2024). Additionally, the complexity of COPD as a multifactorial disease involving inflammation, oxidative stress, and tissue remodeling requires a multifaceted therapeutic approach. Integrating novel treatments with conventional therapies to achieve comprehensive management presents logistical and clinical challenges (Zeng et al., 2020).

7. Conclusion

This review elucidated the pivotal role of DNA methylation and other epigenetic modifications in the development and progression of Chronic Obstructive Pulmonary Dis- ease (COPD). Through a comprehensive analysis, key target genes involved in lung maturation, inflammation, and oxidative stress were identified, demonstrating how hypermethylation contributes to the worsening of COPD. The review also highlighted the potential of emerging therapeutic procedures, such as CRISPR-based epigenome editing and DNA

Vol. 2024 (10) 388 – 402
ISSN 2688-3651 [online]

methyltransferase inhibitors, in providing personalized management of COPD. The investigation into current COPD treatments revealed significant limitations, including their inability to address the underlying molecular mechanisms of the disease and the socioeconomic burden on patients. Advanced genome-editing technologies like CRISPR offer unprecedented precision in targeting epigenetic changes, but challenges such as off-target effects, delivery system development, and the need for personalized approaches must be overcome (Golpon et al., 2001; He et al., 2020; Jill et al., 2015).

The broader significance of this research lies in its potential to shift the model of COPD treatment towards more individualized and targeted interventions. By integrating novel therapeutic methods with conventional pharmacological interventions, there is hope for more comprehensive and effective treatment plans tailored to each patient's specific molecular characteristics. Furthermore, understanding the environmental and lifestyle factors that influence DNA methylation in COPD underscores the importance of preventative measures, such as smoking cessation and environmental regulations, in reducing disease risk and progression.

Ultimately, the exploration of epigenetic modifications provides new insights into the pathogenesis of COPD and identifies potential targets for intervention, paving the way for innovative therapeutic strategies that could significantly improve patient outcomes and quality of life. The continued advancement in precision medicine holds promise for addressing the complex interplay between genetic predispositions and environmental factors, offering a more nuanced understanding of COPD and its management.

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Vol. 2024 (10) 388 – 402
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