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Review

The Function of Histone Modifications in Chronic Obstructive Pulmonary Disease

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Abstract: Numerous genes expression lead to inflammation in the individuals' lungs that have chronic obstructive pulmonary disease (COPD) may be affected by epigenetic alteration. Important epigenetic processes include methylation of DNA and different histones post-translational changes, including ubiquitination, phosphorylation, methylation, SUMOylation and acetylation. Smoking can trigger the enzymes that control these epigenetic changes. According to the majority of publications, both environmental and genetic variables have a substantial role in the development of COPD. Although, the information about COPD epigenetic is not much but, a better perception of the disease pathophysiology and identifying new markers to create novel therapeutics for patients can be achieved via a better understanding of the epigenetic processes involved.

Keywords: Post-translational modifications, Epigenetics, Histone Phosphorylation, Histone Ubiquitination, Histone methylation, inflammation, proinflammatory cytokines, DNA methylation, COPD

1. Introduction

An increasing number of people throughout the world are suffering with COPD, and it is responsible for a disproportionate share of the healthcare dollar bill in both direct and indirect costs (1,2). From the fourth biggest cause of death worldwide in 2004 to the third major incidence of death in 2030, (COPD) is predicted by WHO (3-5). Progressive, irreversible airflow restriction is a hallmark of COPD, This is brought on by chronic inflammation in the bronchi and lungs due to exposure to harmful substances like cigarette smoke (6). Cigarettes contain around 4700 active ingredients and 1014 free radicals, the intake of which is largely responsible for the pathophysiology of COPD. Cell death, insufficient regeneration, the oxidant-antioxidant ratio, the concept of elastase-antielastase and chronic inflammation, these factors are all assumed to have a role in the progression of COPD (7). Many people believe that the inflammation brought on by smoking cigarettes is the primary cause of COPD. Involvement of elevated expression of of several other cytokines, which are proinflammatory factors, is thought to be involved in the underlying mechanism (8-10). Recent years have seen significant advancements in our knowledge of the molecular biology underlying activation of inflammatory genes and the methods by which they may be turned off, both have potential use in the management of inflammatory lung disorders. (11). Epigenetic modifications have been linked to the onset of chronic inflammation by modulating gene expression of proinflammatory cytokines like oncogenes, tumor suppressors, tumor necrosis factor alpha (TNF-α) the transcription factor nuclear factor kappa B (NF-kB) activation and interleukins (12-15). Deficient deacetylation or

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excessive acetylation, for instance, may cause the activator protein 1 (AP-1) and the nuclear factor kappa B (NF-kappa B) controlled gene transcription of proinflammatory genes, leading to an inflow of more proinflammatory cells and a perpetuation of the inflammatory cycle (8). In addition, newer research has revealed that the widely used corticosteroids in the treatment of COPD may operate in part through epigenetic mechanisms (16,17). By inhibiting these transcription factors and their potential to promote histone alterations and chromatin remodeling, the inflammatory genes are thought to be turned off by corticosteroids, which seems to reduce inflammation. (18). Heritable changes in gene expression that are not coded in the DNA sequence itself but rather by post-translational modifications in DNA and histone proteins are referred to as epigenetics. Epigenetics is the word used to describe these types of alterations (19,20). Methylation of DNA, that prevents genes from being copied, and alterations to the histone proteins, which DNA loops across, both work to silence transcription, are two of the most important epigenetic processes, respectively (12,21). Chromatin's fundamental unit is the nucleosome, and it consists of a little piece of DNA encased in a core histone tail that includes each of H4, H3, and H2A/B in two copies. (22-24). Chromatin may also take on a closed conformation, which is associated to repression of expression (25). Transcription can begin if the structure of chromatin has been broken down, a process that is accomplished by unfolding bare DNA. This is necessary for RNA polymerase to be able to transcribe mRNA from the DNA template. It begins with the binding of activated proinflammatory transcription factors like NF-B to a particular sequence of genes (11). The nucleosome histones are mostly spherical, with the exception of their disordered N-terminal "tails" (26). The covalent alteration of histones is a key epigenetic process for modulating expression of genes. Moreover, N-terminal tails are highly enriched for post-translational modifications such as methylation of lysines and arginines, acetylation, phosphorylation, ubiquitination, SUMOylation, and ADP-ribosylation (27–29). Altering the charge of the core histone can activate or silence gene transcription by shifting the chromatin structure from a closed to an open conformation (11).

The activation of inflammatory genes in COPD can be better understood if the molecular mechanism behind this process is known. Errors in methylation of DNA and alterations in deacetylation and acetylation of histones are, nevertheless, the most commonly detected epigenetic alterations. Possible contributions of a variety of post-translational alterations, including histone methylation, ubiquitination, phosphorylation, deacetylation, acetylation and methylation of DNA in the creation of cutting-edge drugs that can be utilized either alone or in combination with existing treatments for COPD, as well as the disease's development and progression, are reviewed in this report.

2. Chronic Obstructive Pulmonary Disease and Epigenetic alterations

2.1. Methylation of Histone

Over the course of the past four decades, the methylation of histones has been identified as a regulator of gene expression (30). Methylations on arginine and lysine amino acids of histones are among the most stable alterations; as a result, they are thought to be useful markers for transporting epigenetic information that survives cell divisions (31). Methylation of histones H3 and H4 has received the greatest attention. Some of the most common sites for methylation in lysine amino acids of histones are in the position of H4K20, H3K79, H3K36, H3K27, H3K9 and H3K4. Gene activation is connected with H3K4 and H3K36 methylation, while repression is linked to H3K9, H3K27, and H4K20 methylation

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(26,94). On mammalian histones, the presence of arginine methylation has proven to be challenging to identify, in contrast to the methylation of lysine (32). Mono-methylated arginine exists, and di-methylated arginine can be symmetric (me2s) or asymmetric (me2a) (33). Recently, it has become clear that alteration of arginine amino acids by methylation plays a significant role in the management of DNA repairing, RNA biogenesis, cell-to-cell communication. This regulation can occur directly through the regulation of protein function or indirectly through the effect of metabolic byproducts of arginine methylation on nitric oxide (NO)-dependent processes (34,35). Protein arginine methyltransferases (PRMTs) attach one or two methyl groups from AdoMet (S-adenosylmethionine) to the guanidine-nitrogens of arginine, generating an epigenetic signature connected to expression of genes, which is essential in a wide range of biological functions and is suppressible by tiny effectors. (36,37). Six of the nine PRMTs that are encoded by the human genome (PRMT1, 2, 3, 6 and 8) are type I enzymes, according to classifications that may be made of them (33). Protein arginine methyltransferases (PRMTs) are able to precisely methylate arginine residues in proteins, resulting in either monomethylarginine (MMA), symmetric dimethylarginine (SDMA), or asymmetric dimethylarginine (ADMA) (38). Multiple research have looked at the connection between smoking and ADMA levels because of the strong link between the two and COPD. In comparison to nonsmokers, smokers have lower levels of ADMA according to certain research (39–41), while smokers have higher levels of ADMA according to other studies (42). Despite the fact that the results are debatable, it is possible that elevated levels of ADMA in smokers are connected with PRMT operations that are dysregulated. There is evidence that PRMT4, 5, 6, 9, and 10 are all overexpressed at higher levels in COPD lung tissue specimens (43). According to the research of Kohse et al. (44), PRMT2, 4, and 6 may participate in the regulation of Th17 cell development, which may in turn play a part in the inflammatory processes that contribute to COPD. Extremely strong hypoxic stimuli can trigger COPD. In the lungs of mice exposed to hypoxia, Both the PRMT2 and the levels of protein were discovered to be increased, according to Yildirim et al (45). Further evidence implicating oxidative stress in the development of COPD was found when PRMTs were found to be up-regulated in human endothelial cells (46). A recent study published by Andresen et al. (47) found a strong correlation between rising DEFB1 mRNA levels and the development of COPD. These findings prove the presence of PRMTs in COPD models and suggest a possible association between COPD and the methylation of arginine caused by PRMT functioning. Importantly, the exact mechanisms of methylation of histones potential involvement in the aetiology of COPD is unresolved. Methylation of histones in COPD is poorly understood; hence further in vivo and in vitro studies are required to elucidate the mechanisms involved.

2.2. Ubiquitination of Histone

The Ubiquitin-Proteasome System (UPS) has gained significant attention in the field of COPD in recent years. Patients with COPD frequently experience diaphragm and skeletal muscle dysfunction because of an unfavorable muscular protein production ratio to degradation of muscle protein (48-50) The ATP-based ubiquitin-protein degradation (UPS) is a crucial regulator of protein degradation (51). Numerous studies have demonstrated that the UPS is partially activated in COPD patients, which results in increased protein

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breakdown and limb muscle atrophy (52,53). Degradation of contractile proteins in COPD has been linked to the UPS, which is vital for biological functions, such as the reaction to hypoxia (54,55). Skeletal muscle atrophy caused by smoking is linked to increased USP-19 expression through activation of p38 and ERK MAPKs (56). Patients with moderate to severe COPD have been shown to have higher local production of proinflammatory cytokines, which has been connected to the UPS and the lack of myosin in the diaphragm. (57-60). Furthermore, Zou et al (61,62) showed that -TrCP (E3-ubiquitin ligase) actively involved in the pulmonary inflammatory response via histone protein O-palmitoylation. Steroid resistance is related to decreased HDAC2 abundance, which has been shown in patients with COPD and is induced by CSE therapy in epithelial cells, macrophages, and mice lungs (63). The UPS is essential for cell survival and proliferation, and Kim et al. (64) discovered that CSE treatment could increase Akt protein breakdown. Collectively, these findings suggest that UPS aberrant activation is a key factor in the development of COPD. All eukaryotes have ubiquitin, a regulatory protein with 76 amino acids (65). vesicle trafficking, endocytosis, transcriptional regulation, signal transmission, immunological response, DNA repair, stress response, cell-cycle control and Protein degradation are only some of the physiological activities regulated by ubiquitination post-translational modification to target proteins (66,67). To guarantee the prompt and effective proteolysis of target substrates, the UPS employs a complex network of protein components (ubiquitin-activating E1 enzymes, ubiquitin-conjugating E2 enzymes, ubiquitin-protein E3 ligases, and the 26S proteasome) that function in concert with one another (68,69). The maintenance of genomic stability and transcriptional regulation are two processes that are significantly regulated by the ubiquitination of histones (70). H2A (K119) and H2B (K20 in humans and K123 in yeast) are the most common alteration sites (26). The mono-ubiquitinated H2A (H2Aub) and H2B (H2Bub) histones, which have a single ubiquitin biomolecule attached to the highly conserved lysine amino acids, are the most common kinds of ubiquitinated histones (71). Reports have shown a connection between H2B mono-ubiquitylation and transcriptional activation (72,73). Transcriptional repression, which is achieved by the ubiquitylation of H2A, is critically important (74,75). In addition to their functions in gene expression and DNA repair, the two histone proteins also participate in a wide variety of other cellular activities (76,77). Several human disorders, including cancer, have been linked to abnormalities of histone ubiquitination or deubiquitination (78,79). On the other hand, further investigations are needed to determine if histone ubiquitination has a role in COPD.

2.3. Histone Phosphorylation

There is strong evidence that histone phosphorylation is involved in recombination, replication, DNA repair, cell death and mitosis (80). Histones are phosphorylated at their N-terminal tails mostly but not solely on serines, threonines, and tyrosines (81). Histone H3 phosphorylation during mitosis is regulated by a delicate equilibrium between kinase and phosphatase activity (H3). Depending on the particular stimulus or stress, ribosomal S6 kinase (RSK)-2, mitogen- and stress-activated kinase (MSK)-1, and MAPKs mediate H3 phosphorylation, which stimulates immediate-early gene expression (82). Condensation of chromosomes and transcriptional activity during mitosis are both correlated with H3 phosphorylation at serine amino acid number 10 and 28 (83,84). Transcription of NF-κB-regulated genes (26), which is crucial to the inflammatory response in COPD, has been shown to depend on H3S10 phosphorylation (85,86). The phospho-acetylation of histone H3 on pro-inflammatory gene promoters in response to cigarette smoke stimuli is shown to be

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essential for the transcription of NF-κB, as discovered by Chung et al (92). Additionally, Sundar et al. (87) show that MSK1 is a key downstream kinase involved in cigarette smoke-induced NF-kappaB transcription and phospho-acetylation of H3, both of which are relevant to the COPD pathophysiology. Release of elastolytic enzymes, reactive oxygen species (ROS), chemokines and cytokines from alveolar macrophages is known to have a major role in the pathogenesis of COPD (88,89). Alveolar macrophages from COPD smokers were shown to have an elevation in the phosphorylated form of the p38 subgroup of MAPKs (90). Lung macrophages rely heavily on the p38 MAPK pathway to generate inflammatory cytokines (91,92). In addition, reactive oxygen species (ROS) may contribute to heightened inflammation by activating and phosphorylating MAPKs (93). This suggests that cigarette smoke may activate kinases, which in turn may phosphorylate histones, leading to transcription of inflammatory genes. The chronic inflammatory response triggered by cigarette smoke is linked to a number of diseases, including COPD, and these kinases may be therapeutic targets for treating these conditions.

2.4. Histone Acetylation and Deacetylation

Cigarette smoke is a major risk factor in the evolving of COPD because it activates transcription of inflammatory genes (94,95). One of the most important mechanisms controlling the specificity and persistence of transcription is acetylation and deacetylation of histone (8). The acetylation of histones is critical for remodelling the chromatin and has been related to an extended inflammatory reaction in the lungs of individuals suffering from COPD (96,97), and is induced by cigarette in macrophages and in the lung of humans and rats. According to studies, cigarette smoke exposure increases H3 and H4 acetylation around the proinflammatory genes promoters in mouse lungs, resulting in a more robust inflammatory response (92). Enhancing the transcription of NF-κB-dependent inflammatory genes (14,96) is a result of the histones acetylation by histone acetyltransferases (HATs), which allows TFs like NF-κB to reach the promoter section. Histone deacetylation by HDACs, on the other hand, stops gene transcription by making DNA more twisted, which makes it harder for transcription factors81 to reach. As a result, the equilibrium between histone acetylation and deacetylation is crucial for controlling inflammatory gene expression. When the equilibrium is disrupted, proinflammatory genes regulated by AP-1 and NF-kB may be continuously transcribed, resulting in an inflow of even more proinflammatory cells and a vicious cycle of chronic inflammation (97,98).

2.5. HATs

Multiple histone acetyltransferases (HATs) have been discovered and characterized, and it has been established that these enzymes acetylate distinct locations on histones and other proteins, including transcription regulators (99). By comparing their biological functions and the degree of conservation in the HAT domain, we may classify them into three distinct families (100). Between all of the HATs, CBP/p300 has received the most attention (101). It has a significant role in controlling the production of proinflammatory cytokines, namely via the mitogen-activated protein kinase (MAPK), NF-κB, and signal transducers and activators of transcription (STAT) (102). Both hydrogen peroxide (H2O2) and tumour necrosis factor alpha (TNF-alpha) have been found to induce histone acetylation (HAT activity) in alveolar epithelial cells, suggesting a role for both stimuli in the cigarette smoke-mediated inflammatory response (103). The continuous proinflammatory response found in COPD is due to the increased NF-B, H3 and H4 acetylation by the means of CBP/p300, which

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is mediated by cigarette (104). Numerous detrimental respiratory health effects, including COPD, have been linked to diesel exhaust particles (DEP). Important functions of the cyclooxygenase-2 (COX-2) gene are regulated by histone acetyltransferase (HAT) p300, which may be recruited to the gene's promoter by exposure to DEP (105,106).

2.6. HDACs

Humans have 18 histone deacetylases (HDACs), which may be further broken down into four groups defined by their unique structural characteristics and regulatory processes (107). HDAC1, 2, 3, 8 and 11 are members of class I and are transcribed in all of cells ubiquitously, suggesting that they might have a role in controlling the proliferation of the cells (108). HDAC4, 5, 6, 7, 9, and 10 are members of class II, and are produced with varying degrees of tissue selectivity and might have a role in differentiation of the cells (109). The seven members of Class III HDACs, often known as sirtuins, are designated as Sirt1-7 (110). HDAC11, the single class IV member, resembles HDACs from the class I and II (111). Histone deacetylases (HDACs) are key epigenetic regulators that govern the activation of nonhistone proteins (112), like NF-B, and, consequently, have the capacity to regulate NF-B-dependent proinflammatory gene transcription (113) by removing acetyl from the -N-acetyl lysine residues on histones. Cigarette smokers with COPD had dramatically decreased levels and activity of histone deacetylases, especially HDAC2 (114). It has been shown that the expression of HDAC2 (18) is drastically reduced (by 95%!) in individuals with very severe illness (GLOD stage 4). The Total function of HDAC is reportedly lowered in the tissues of bronchial-biopsy alveolar macrophages and peripheral lung tissue samples in individuals suffering from COPD, and this drop is connected with the intensity of the illness and inflammatory reaction, according to Ito et al (129). It has been demonstrated by Chen et al. (115) that HDAC activity is reduced in the PBMC of people with COPD compared to the PBMC of healthy controls. Additionally, after activating airway epithelial cell lines and alveolar macrophages with inflammatory boost, TSA, a nonselective inhibitor of HDAC, can result in an increase in the expression of inflammatory genes including AP-1 and NF-κB (116,117). Therefore, cigarette smoke alters HDACs, leading to acetylation of histones, which amplifies the inflammatory response and accelerates the development of COPD. oxidative stress, as shown in the lungs of COPD patients, lowers HDAC2 activity and expression (118). Cigarette smoke condensate (CSC) was found to lower the levels of HDAC2 and HDAC function in A549 cells and to drastically enhance acetylation of histone H4 proteins. Protein alteration by aldehydes and nitric oxide products also contributed to the reduction in HDAC2 activity (119). The discovery that a number of proinflammatory mediators, including heat shock proteins, matrix metalloproteinases, monocyte chemoattractant protein-1, IL-1, TNF, IL-6, IL-8 and intercellular adhesion molecule-1 (ICAM-1) are elevated in the smokers BAL fluid and may also be promoted by inhibiting deacetylases in histones (11), supports ROS and CSC-mediated reduction of HDAC2. COPD is characterised by resistance to the effects of corticosteroids and heightened inflammation, both of which are caused by decreased HDAC activity (16,120). Corticosteroids' primary function is to inhibit the expression of proinflammatory TFs such as NF-kB and AP1 (12), which control the expression of numerous inflammatory genes. These genes are responsible for producing cytokines, chemokines, adhesion molecules, inflammatory enzymes, and receptors. Since histone deacetylase 2 (HDAC2) inactivation is essential for transrepressive functionality of the glucocorticoid receptor (GR), that mediates anti-inflammatory impact of corticosteroids, it is a major contributor to the development of corticosteroid resistance (121). Therefore,

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corticosteroids and lower HDAC2 activity inhibit inflammatory genes by recruitment of HDAC2 to activated inflammatory genes; expression is downregulated in several conditions where patients have a poor response, including chronic obstructive pulmonary disease (COPD) (12). In addition, Ito et al. (122) found that overexpressing HDAC2 in glucocorticoid-insensitive COPD alveolar macrophages restored glucocorticoid sensitivity. During oxidative stress, tyrosine residues in the active region of HDAC2 may be nitrated or phosphorylated, leading to a loss of function before HDAC2 is degraded by the proteasome, resulting in a decrease in HDAC2 activity and expression (123). The possibility of reversal of COPD's corticosteroid resistance, which was previously mentioned, has implications for the creation of innovative treatments for this condition that responds poorly to current treatments.

3. DNA methylation

Multiple studies, both of individual genes and of the entire genome, have linked DNA methylation alterations to cigarette smoking, suggesting that these alterations may contribute to the development of diseases like COPD. DNA methylation appears to have an important role in the development and progression of COPD (124). Comparing induced sputum from COPD patients to that of healthy participants, Guzmán et al. (125) discovered a higher proportion in methylation of promoter in CDKN2A and MGMT genes in individuals suffering from COPD. These methylations are substantially related to heavy smoking. Site-specific and dynamic methylation alterations in the reaction to cigarette might contribute to protracted hazards linked with cigarette, which remain after smoke quitting, as shown by Wan et al. (126). This may provide some insight into the steady decline in health despite quitting smoking. Methylation of DNA might have a function in pulmonary inflammation, as shown by the work of Monick et al. (127), who showed that smoking may alter methylation of DNA in macrophages of lung alveolar and lymphoblasts. Methylation of DNA is linked to both C-reactive protein (CRP) levels and smoking which is a biomarker of systemic inflammation, in Alpha-1 antitrypsin (AAT)-deficient people, as shown in other investigations as well (128). The systemic effects of COPD and smoking can also be better understood via profiling of methylation in DNAs with the source of white blood cell (124). Therefore, it is possible for us to draw the conclusion that smoking cigarettes can raise the degree of methylation of DNA that is implicated at both systemic and local inflammation that is associated with COPD. Some researchers have hypothesised that oxidative stress is involved in the process. The proinflammatory responses in respiratory disease have been shown to be influenced by oxidative stress through its effects on chromatin remodelling and signal transduction (129). Tobacco smoke contains a wide variety of chemical compounds and free radicals, such as semiquinones and reactive aldehydes, which are known to produce oxidative stress in the lungs (130,131). Increased levels of oxidative stress can cause DNA methyltransferase 1 (DNMT1) expression and activity, which can then influence DNA promoter methylation and, ultimately, gene expression (132-135). The specific function of oxidative stress in methylation of DNA in COPD will be determined in future research, which will lead to the discovery of novel pathophysiological processes and epigenetic targets of gene expression in this disease. A major epigenetic change that has a major impact on how genes are expressed is DNA methylation, which occurs in a variety of different ways and is studied extensively (136,137). About half of all genes that produce protein have GC-rich sections in the promoter named CpG islands (19,27). methylation of DNA is the covalent insertion of a methyl agent in the position 5 of a cytosine (138,139). Methylation of CpG

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dinucleotides is a crucial epigenetic process for controlling the expression of genes in certain tissues and the differentiation of cells (140). Up to 80% of mammalian CpG dinucleotides are thought to have methylated (141). Unmethylated CpG residues are primarily found in the promoters of active genes (20). Methyl-binding proteins (MBPs) have a function in identifying and interpreting methylation patterns (142-146), while DNA methyltransferases (DNMTs) are in charge for enzymatically adding the methyl group to DNA in mammals. Mammalian DNMTs are divided into two classes: those that de novo methylate DNA and those that keep the methylation status constant. These four classes are designated DNMT 1, 2, 3A, and 3B (147). When it comes to mammalian species, DNMT1 is by far the most prevalent DNA methyltransferase (a maintenance methyltransferase) at the protein level (22). It has been shown that ablation of DNMT2 in the embryonic stem cells of mouse had no discernible result on methylation of DNA (20), suggesting that DNMT2 in mammals has very low or no DNMT activity. De novo methyltransferases 3A and 3B catalyse the creation of new methyl groups in DNA. In general, gene silencing occurs when CpG islands in promoters become hypermethylated (148,149), whereas active transcription occurs when CpG islands become hypomethylated (13,150). The inactivation of transcription that occurs as a result of changes to DNA methylation has been proposed to be explained by two different mechanisms. There are specific and nonspecific factor binding sequences in promoter regions that play a role in regulating gene activity. Interfering with the process by which transcription factors bind to specific sites might be thought of as one potential mechanism for this effect (151). The second approach relies on the discovery that MBPs have a methyl-CpG binding domain, which allows them to bind selectively to methylated DNA (152). Histone deacetylases 1 and 2 (HDAC1 and 2) are recruited when MBPs engage with the corepressor Sin3A, leading to transcriptional repression (153). An increasing number of human disorders are due to aberrant regulation of DNA methylation, highlighting the significance of this process (154).When it comes to apoptosis in COPD, DNA methylation is just as important as inflammation. Researchers have found that apoptosis plays a significant part in the progression of COPD (155,156). The lungs of the people suffering from COPD show a boost in apoptosis in the airway epithelial, alveolar, and endothelial cells (157-159). Smoking may promote pulmonary vascular endothelial apoptosis in COPD by reducing the cyclooxygenase (COX)-2 functionality and production in the pulmonary vascular endothelial cells, as shown in our prior studies (160). Additionally, this is linked to an alternation in methylation of a CpG island in the mitochondrial transcription factor (mtTFA) promoter region. Moreover, the demethylating drug 5-azacytidine (5-AZA) can inhibit COX-2 expression and activity (161,162) (Figure 1). Cell proliferation, differentiation, and survival are all controlled by the mitogen-activated protein kinase (MAPK) superfamily, of which extracellular signal-regulated kinase (ERK) is a subfamily (163,164). The expression of ERK was shown to be considerably higher in smokers in both in vivo and in vitro experiments (165,166). Ginkgo biloba extract protects human pulmonary artery endothelial cells (HPAECs) against cigarette smoke extract-induced apoptosis through ERK signalling, as shown by Hsu et al. (167). According to recent studies, the ERK pathway has been shown to have a role in the regulation of DNA methylation (168,169). Finally, DNA methylation regulation by smoking is a mechanism through which cigarette smoking might trigger cell death in chronic obstructive pulmonary disease. Thus, it is worthwhile to explore the underlying molecular process in depth, and it may become a possible treatment target for COPD.

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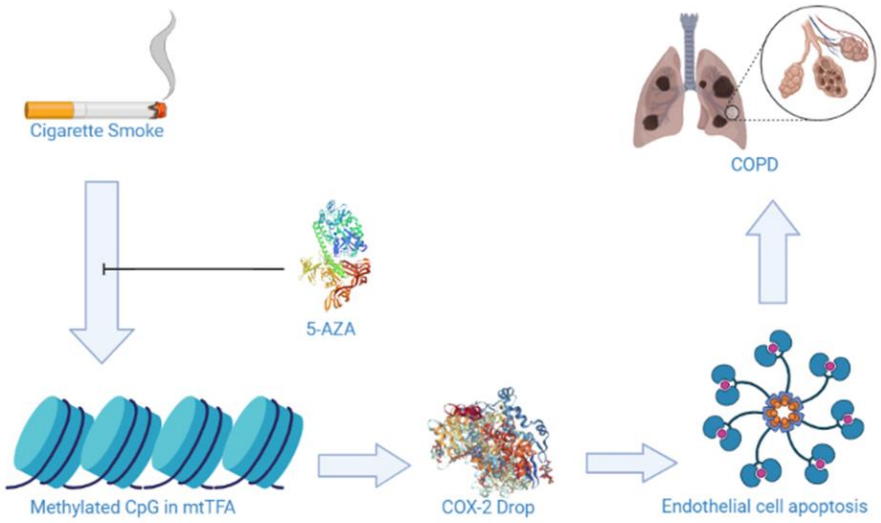

Figure 1. The promoter methylation of the mtTFA gene can be triggered by cigarette smoking. Modifications in mtTFA gene methylation may mediate pulmonary vascular endothelial apoptosis in chronic obstructive pulmonary disease (COPD) via reducing COX-2 production and activity in PVE cells. 5-AZA is capable of reversing this methylation state.

4. Conclusions

The changes brought on by smoking in the enzymes and chemicals that alter histones and methylate DNA can influence many different physiological processes, including gene expression of inflammatory mediators, post-translational alternations of histones, apoptosis, cell cycle arrest, reactions of unfolded protein, senescence, antioxidants or stress reaction, DNA replication/recombination/repair, autophagy, tumour suppressor genes and growth factors (94). It is possible that smoking leads to epigenetic changes that may be passed down from generation to generation, and their relevance to COPD has become increasingly obvious in recent years. Analyzing alternations in methylation of DNA and histone modifications is essential for learning more about the bio-molecular basis of COPD. Nevertheless, the bio-molecular processes are not well known at this time. These epigenetic alterations are theoretically reversible, which may result in the development of new drugs for COPD patients or strategies for halting the advancement of this illness when it is diagnosed at an early stage.

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