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Epigenetic mechanisms in chronic obstructive pulmonary disease

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Abstract. – Epigenetic modification may affect the expression of multiple inflammatory genes in lungs of patients with chronic obstructive pulmonary disease (COPD). Major epigenetic events include DNA methylation and various post-translational modifications of histones, such as histone methylation, acetylation, phosphorylation, ubiquitination, and sumoylation. Enzymes which regulate these epigenetic modifications can be activated by smoking. Both environmental and genetic factors play significant effect in development of COPD which have been reported by most references; however, little is known about the epigenetic pathways involved in the disease. Understanding the epigenetic mechanisms can help us clarify the pathogenesis of COPD and identify novel targets for developing new therapies for patients with COPD.

Key Words:
COPD, Epigenetics, DNA methylation, Histone methylation, Acetylation, Phosphorylation, Ubiquitination.

Introduction

Chronic obstructive pulmonary disease (COPD) is a major and increasing global health problem with enormous amount of expenditure of indirect/direct healthcare costs[1,2]. The World Health Organization (WHO) has predicted a rise of COPD mortality, from the fourth leading cause of death in 2004 to the third in 2030[3-5]. COPD is characterized by a poorly reversible airflow limitation that is usually progressive and associated with a chronic inflammatory response in the airways and the lung to noxious particles or gases, particularly cigarette smoke[6]. Cigarette smoke which contains more than 10^{14} free radicals/oxidants and 4700 chemical compounds are the main cause for the pathogenesis of COPD. The proposed pathogenesis of COPD includes elastase-antielastase hypothesis, chronic inflammation, oxidant-antioxidant balance, apoptosis and ineffective repair[7]. Inflammation that triggered by cigatette smoking is considered to play a central role in the development of COPD. The underlying mechanism likely involves increased expression of a range of proinflammatory cytokines and chemokines[8-10]. Recently, much more has been learned about the molecular and cell biology that account for switching on inflammatory genes and even more about mechanisms for switching off those genes that can be useful in therapy of inflammatory lung diseases[11]. Reports indicated that epigenetic modifications may mediate development of chronic inflammation by modulating the expression of proinflammatory cytokine TNF-α, interleukins, tumor suppressor genes, oncogenes and autocrine and paracrine activation of the transcription factor nuclear factor-κB (NF-κB)[12-15]. For example, disruption of the acetylation: deacetylation balance may lead to sustained gene transcription of proinflammatory genes controlled by nuclear NF-κB and AP-1, resulting in a further influx of proinflammatory cells, creating a chronic cycle of inflammation[8]. Moreover, recent studies suggested that corticosteroids, which are used extensively in the treatment of COPD, may work partly via epigenetic mechanisms[16,17]. Corticosteroids appear to suppress inflammation by switching off the inflammatory genes by targeting these transcription factors and their ability to induce histone modifications and chromatin remodeling[18].

Epigenetics is the term used to describe heritable changes in gene expression that are not coded in the DNA sequence itself but by post-translational modifications in DNA and histone proteins[19,20]. The key epigenetic mechanisms are DNA methylation, which represses gene transcription, and modification of core histones around which DNA is wound in the chromosome and resulting in either activation or repression of genes[12,21]. The basic unit of chromatin, the nucle-

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osome, consists of a short segment of DNA wrapped around core histones made up of two copies of H2A, H2B, H3, and H4[22-24]. This conformation of chromatin structure is described as closed and is associated with suppression of gene expression[25]. Gene transcription occurs only when the chromatin structure is open up with unwind naked DNA, so that RNA polymerase II can transcribe mRNA from the DNA template. The process is initiated when the activated proinflammatory transcription factors, such as NF-κB, bind to a specific DNA sequence[11]. The core histones are predominantly globular except for their N-terminal ''tails,'' which are unstructured[26]. The covalent modification of histones is an essential epigenetic mechanism of gene regulation. These post-translational modifications (methylation of lysines and arginines, acetylation, phosphorylation, ubiquitination, SUMOylation, and ADP-ribosylation) occur most frequently at the N-terminal tails[27-29]. Change in the electrical charge of core histone results in transformation of chromatin structure from the closed conformation to the open form[11], and results in either activation or inhibition of gene transcription.

Understanding of the molecular mechanism helps explain how inflammatory genes become activated in COPD. However, the most frequently observed epigenetic changes include aberrant DNA methylation, and histone acetylation and deacetylation. In this chapter, we focus on the role of DNA methylation, histone methylation, acetylation and deacetylation, phosphorylation and ubiquitination in the development and progression of COPD and speculate on their potential role for the development of novel therapeutics that will serve as direct or adjuvant therapeutic compounds in the treatment of the disease.

Epigenetic Modifications and COPD

DNA Methylation

Many single gene and genome wide studies provide evidence that changes in DNA methylation are associated with cigarette smoking and may be causes of smoking associated illness, such as COPD. There is strong evidence towards about key role of DNA methylation in both the presence and severity of COPD[30]. Guzmán et al[31] found a high percentage of CDKN2A and MGMT promoter methylation in induced sputum from COPD patients compared with healthy subjects, and they are strongly associated with heavy smoking. Wan et al[32] declared that changes in genome-wide methylation can be found in COPD, and dynamic, site-specific methylation changes in response to smoking which may contribute to the extended risks associated with cigarette smoking that persist after cessation. This may help to explain why the disease worsens progressively even after smoking cessation. Monick et al[33] demonstrated that smoking can affect DNA methylation in both lymphoblasts and pulmonary alveolar macrophages, suggesting that DNA methylation may play a role in pulmonary inflammation. Other studies also show that DNA methylation is associated with cigarette smoking and C-Reactive Protein (CRP) levels, a biomarker of systematic inflammation, in Alpha-1 antitrypsin (AAT)-deficient subjects[34]. In addition, methylation profiling in white blood cell source DNA may provide important insights into the systemic impact of COPD and smoking[30]. Thus, we may concluded that cigarette smoking can increase the level of DNA methylation, which is involved in the local and systematic inflammation of COPD. The mechanism may be associated with oxidative stress. It has reported that oxidative stress can modulate chromatin remodelling and signal transduction, which affects proinflammatory responses in the respiratory disease[35]. Cigarette smoke, a complex mixture of oxidants/free radicals and different chemical compounds that include reactive aldehydes and semiquinones is known to cause oxidative stress in the lungs[36,37]. Oxidative stress can up-regulate the expression and activity of DNA methyltransferase 1 (DNMT1) and induce DNA promoter methylation, in turn, affect the expression of the genes[38-41]. Future studies to determine the precise role of oxidative stress in DNA methylation in COPD will identify new pathophysiological mechanisms and epigenetic targets of gene expression in COPD.

DNA methylation is one of the main epigenetic modifications which played a significant effect that controls gene expression[42,43]. DNA methylation is the covalent addition of a methyl group in the position 5 of a cytosine (C)[44,45], and approximately 50% of protein coding genes have GC-rich areas of DNA in their promoter regions that are known as CpG islands[19,27]. Modification of CpG dinucleotides by methylation is an important epigenetic mechanism involved in the regulation of tissue specific gene expression and cellular differentiation[46]. It has been estimated that as much as 80% of all CpG dinucleotides in the

mammalian genome are methylated[47]. The remaining unmethylated CpG residues are mostly located in the promoter regions of constitutively active and/or inducible genes[20]. The mammalian DNA methylation machinery consists of two components: DNMTs, which are responsible for the enzymatic addition of the methyl group, and methyl-binding proteins (MBPs), which play a role in the methylation pattern identification and interpretation[48-52]. Two groups of mammalian DNMTs, one that *de novo* methylates DNA, and the other that maintains the methylation status, are classified as four different types: DNMT 1, 2, 3A and 3B[53]. DNMT1 is a maintenance methyltransferase and is the most abundant DNA methyltransferase in mammals[22]. Mammalian DNMT2 has little or no DNMT activity and deletion of DNMT2 in mouse embryonic stem cells had no noticeable effect on DNA methylation[20]. DNMT 3A and 3B are *de novo* methylation enzymes[53]. Hypermethylation of CpG islands in gene promoters generally leads to gene silencing[54,55], and hypomethylation results in active transcription[13,56]. There are two hypotheses that may explain transcriptional inactivation from DNA methylation. The promoter regions contain sequences that bind both specific and general factors important for gene activity and regulation. One potential mechanism is through interfering with the binding of transcription factors to such sites[57]. The other mechanism is based on the finding that MBPs specifically bind to methylated DNA through a methyl-CpG-binding domain[58]. MBPs can interact with the corepressor Sin3A to recruit histone deacetylase 1 and 2 (HDAC1 and 2), which in turn results in transcriptional silencing[59]. The importance of DNA methylation is highlighted by the fact that a growing number of human diseases results from abnormal control[60].

Besides to inflammation, DNA methylation also participates in apoptosis in COPD. Recent studies have highlighted the role of apoptosis in the development of COPD[61,62]. An increase apoptosis in airway epithelial, alveolar and endothelial cells is found in the lung of COPD patients[63-65]. Our previous studies find that cigarette smoking can decrease the expression and activity of cyclooxygenase (COX)-2 in the pulmonary vascular endothelial cells, which might mediate the pulmonary vascular endothelial apoptosis in COPD[66]. And this is associated with altered methylation status of a CpG island in the promoter region of mitochondrial transcription factor A (mtTFA). Furthermore, the demethylating agent 5-azacytidine (5-AZA) can reverse the expression and activity of COX-2[67,68] (Figure 1). Extracellular signal-regulated kinase (ERK) is one group of the mitogen-activated protein kinase (MAPK) superfamily that control several fundamental cellular processes, driving proliferation, differentiation and cell survival[69,70]. Both *in vivo* and *in vitro* experiments, the expression of ERK was significantly increased in smokers[71,72]. Hsu et al[73] find that *Ginkgo biloba* extract confers protection from cigarette smoke extract-induced apoptosis in human pulmonary artery endothelial cells (HPAECs) via ERK signaling. Recent reports indicate that DNA methylation is regulated in part by the ERK pathway[74,75]. In conclusion,

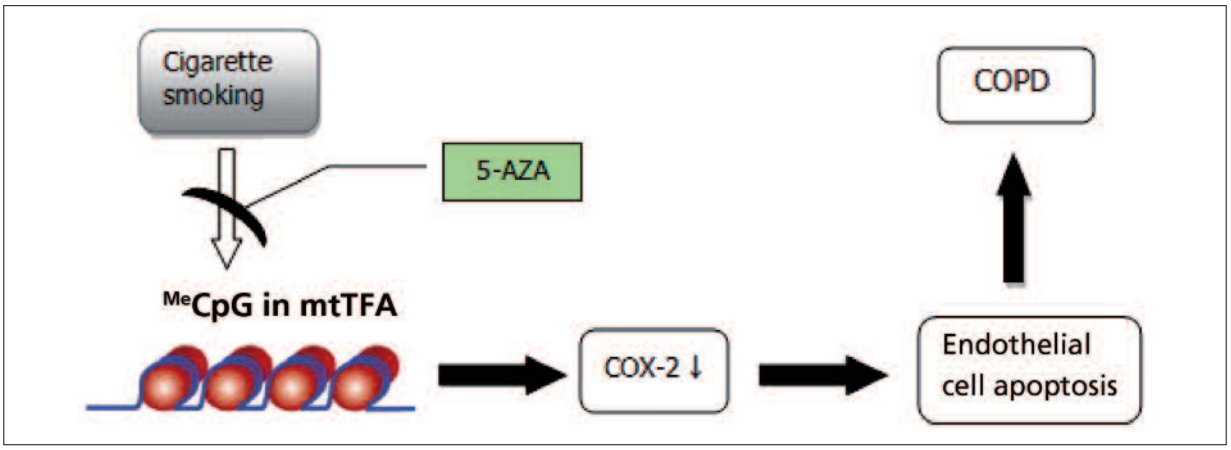

Figure 1. Cigarette smoking can induce the mtTFA gene methylation in the promoter region. Altered mtTFA gene methylation status in turn decreases the expression and activity of COX-2 in the pulmonary vascular endothelial cells, which might mediate the pulmonary vascular endothelial apoptosis in COPD. This methylation status can be reversed by5-AZA.

cigarette smoking can induce cell apoptosis in COPD through regulating DNA methylation. Therefore, the underlying molecular mechanism is worthwhile to study intensively and is, thus, becomes a potential therapeutic target for COPD.

Histone Acetylation and Deacetylation

In the development of COPD, cigarette smoke is the most important risk factor by inducing proinflammatory gene transcription[76,77]. Histone acetylation and deacetylation is a key regulator of the specificity and duration of gene transcription[8]. Cigarette smoke induces acetylation of histone H3 in macrophages and in lung of humans and rodents, which implies that histone acetylation plays a vital role in chromatin remodeling, and is subsequently associated with sustained lung inflammatory response in patients with COPD[78,79]. Reports have shown that there is increased acetylation of histone H3 and H4 near the promoters of proinflammatory genes in rodent lungs in response to cigarette smoke exposure, leading to heightened inflammatory response[76]. The acetylation of histones by histone acetyltransferases (HATs) promotes transcription factors, including NF-κB, to access the promoter region, and resultes in enhanced expression of NF-κB-dependent inflammatory genes[14,80]. In contrast, histone deacetylation by HDACs represses gene transcription by promoting DNA winding thereby limiting its accessibility to transcription factors[81]. Hence, histone acetylation/deacetylation balance plays an important role in regulating the inflammatory gene expression. Disruption of the balance may lead to sustained gene transcription of proinflammatory genes controlled by NF-κB and AP-1, resulting in a further influx of proinflammatory cells, creating a chronic cycle of inflammation[8,82].

HATs

A variety of HATs (histone acetyltransferases) have now been identified and shown to acetylate different sites on histones as well as on non-histone proteins, including transcription regulators[83]. They can be divided into three main families based on sequence conservation within the HAT domain and similarities in their biological function[84]. CBP/p300 is the most extensively studied among the HATs[85]. It is vital for coordinating the expression of proinflammatory cytokines, particularly through MAPKs, NF-κB, and signal transducers and activators of transcription (STAT) pathways[86]. It has shown that both H_2O_2 and TNF-α, relevant stimuli for cigarette smoke-mediated inflammatory response, caused an increase in histone acetylation (HAT activity) in alveolar epithelial cells[87]. Increased acetylation of histone (H3/H4) and NF-κB by CBP/p300 is associated with cigarette smoke-mediated proinflammatory cytokine release, which is responsible for the sustained proinflammatory response seen in COPD[88]. Diesel exhaust particles (DEP) has been associated with numerous adverse respiratory health outcomes including COPD. DEP exposure can induce recruitment of histone acetyltransferase (HAT) p300 to the promoter of the cyclooxygenase-2 (COX-2) gene[89], which play important roles in COPD[90].

HDACs

There are 18 HDACs (histone deacetylases) in the human, and are subdivided into four classes based on specific structural features and distinct regulative mechanisms[91]. Class I comprise HDAC1, 2, 3, 8 and 11 which are ubiquitously expressed in all cells and may be significant in regulating proliferation[92]. Class II includes HDAC4, 5, 6, 7, 9and 10 and they are expressed with a certain grade of tissue specificity and may be involved in cell differentiation[93]. Class III HDACs are also called sirtuins, consists of seven members, Sirt1-7[95]. HDAC11, which is the sole member of class IV, shares similarities with both class I and class II HDACs[95]. HDACs, enzymes that remove acetyl groups from -*N*-acetyl lysine amino acids on histones to suppress gene expression in most cases, are important epigenetic factors that also regulate the activation of nonhistone proteins[96], such as NF-κB and, thereby, have the ability to regulate NF-κB-dependent proinflammatory gene transcription[97]. The levels and activities of histone deacetylases, particularly HDAC2, are reduced significantly in smokers with COPD[98]. In patients with very severe disease (GLOD stage 4), there is a 95% reduction in the expression of HDAC2[18]. Ito et al[35] report that total HDAC activity is decreased in samples of peripheral lung tissue, alveolar macrophages, and bronchial-biopsy specimens from patients with COPD and this decrease is correlated with disease severity and the intensity of the inflammatory response. Chen et al[99] also confirmed that HDAC activity in the peripheral blood mononuclear cells (PBMC) of COPD is lower than that in healthy controls. In addition, TSA, a nonselective inhibitor of HDAC, can lead to increased expression of inflammatory genes, such as AP-1

and NF-κB, in alveolar macrophages and airway epithelial cell lines after activation with inflammatory stimuli[100,101]. Therefore, alteration of HDACs by cigarette smoke leads to acetylation of histones, resulting in amplification of the inflammatory response as COPD progresses.

Oxidative stress can inhibit HDAC2 activity, and chronic oxidative stress, as seen in the lungs of patients with COPD, caused both reduced HDAC2 activity and expression[102]. It has reported that cigarette smoke condensate (CSC) significantly increased acetylation of histone H4 proteins and were associated with decreased HDAC activity and HDAC2 levels in A549 cells. Also, the decreased HDAC2 activity was due to protein modification by aldehydes and nitric oxide products[103]. Reactive oxygen species (ROS) and CSC-mediated inhibition of HDAC2 levels is also supported by the observations that various proinflammatory mediators such as intercellular adhesion molecule-1 (ICAM-1), IL-8, IL-6, TNF-α, IL-1, monocyte chemoattractant protein-1, matrix metalloproteinases and heat shock proteins are increased in BAL fluid of smokers, and also can be induced by inhibition of histone deacetylases[11].

Reduced HDAC activity also accounts for the amplified inflammation and resistance to the actions of corticosteroids, a characteristic feature of COPD[16,104]. The major action of corticosteroids is to switch off multiple activated inflammatory genes that encode for cytokines, chemokines, adhesion molecules, inflammatory enzymes, and receptors, which are regulated by proinflammatory transcription factors, such as NF- kB and AP-1[12]. This corticosteroid resistance is largely caused by inactivation of histone deacetylase 2 (HDAC2), which is critical for the transrepressive activity of the glucocorticoid receptor (GR) that mediates the antiinflammatory effect of corticosteroids[105]. So, recruitment of HDAC2 to activated inflammatory genes is a major mechanism of inflammatory gene repression by corticosteroids and reduced HDAC2 activity, and expression is reduced in some diseases where patients respond poorly[12], such as COPD. In addition, Ito et al[106] report that overexpression of HDAC2 can restore glucocorticoid sensitivity in alveolar macrophages from glucocorticoid-insensitive COPD. The reduction in HDAC2 activity and expression by oxidative stress may relate to nitration or phosphorylation of tyrosine residues within the active site of HDAC2, possibly leading to an initial loss of activity before HDAC2 degradation in the proteasome[107]. As discussed above, the corticosteroid resistance of COPD is potentially reversible, and it has implications for the development of novel therapy for this poorly responsive disease.

Histone Methylation

Histone methylation was first discovered over 40 years in control of gene expression[108]. Among the various modifications, histone methylations at lysine and arginine residues are relatively stable and are, therefore, considered potential markers for carrying the epigenetic information that is stable through cell divisions[109]. Histone H3 and H4 methylation has been most studied. Lysine methylation on histones often occurs at H3K4, H3K9, H3K27, H3K36, H3K79, and H4K20. Among them, methylation at H3K4, H3K36, and H3K79 is linked to gene activation, whereas H3K9, H3K27, and H4K20 methylation is associated with gene repression[26,78]. Unlike lysine methylation, the occurrence of arginine methylation has been difficult to detect on mammalian histones[110]. Arginine can be mono- or di-methylated, the latter is either in a symmetric (me2s) or asymmetric form (me2a)[111]. The methylation of arginine residues has recently come into light as an important posttranslational modification involved in the regulation of RNA processing, signal transduction, and DNA repair, either by the direct regulation of protein function or by metabolic products originating from protein arginine methylation that influence nitric oxide (NO)-dependent processes[112,113]. Methylation of histone arginine residues is an epigenetic mark related to gene expression that is implicated in a variety of biological processes and can be reversed by small-molecule modulators of protein arginine methyltransferases (PRMTs), which add one or two methyl groups from AdoMet (*S*-adenosylmethionine) to the guanidine-nitrogens of arginine[114,115]. The human genome encodes 9 characterized PRMTs which can be classified into two types, 6 of which (PRMT1, 8, 2, 3, 4 and 6) are type I enzymes[111]. PRMTs can specifically methylate protein-incorporated arginine residues to generate protein-incorporated monomethylarginine (MMA), symmetric dimethylarginine (SDMA), or asymmetric dimethylarginine (ADMA)[116].

As COPD is closely related with cigarette smoking, several studies have investigated the relationship between cigarette smoking and ADMA levels. Some studies have found an decrease

level of ADMA in smokers as compared to non-smokers[117-119], while others have detected increased amounts of ADMA in cigarette smoking subjects[120]. Although the results are controversial, altered ADMA levels in smokers might be associated with dysregulated PRMT activities. Some research has shown that the mRNA expression levels of PRMT4, 5, 6, 9, and 10 were up-regulated in COPD lung tissue specimen[121]. Kohse et al[122] found PRMT2, 4, and 6 might play a regulating role in Th17 cell differentiation and for this reason might also be involved in the inflammatory processes that occur in COPD. Hypoxia is a potent stimulus for COPD. Yildirim et al[123] confirmed that PRMT2 mRNA and protein levels were up-regulated in lungs of mice subjected to chronic hypoxia. In addition, PRMTs were shown to be up-regulated in response to oxidative stress in human endothelial cells[124], which plays a key role in the pathogenesis of COPD. Andresen et al[125], recently, report that the overall levels of H3K4me3 were significantly correlated with increasing levels of DEFB1 mRNA, which is associated with the progression of COPD. These results demonstrate that PRMTs are expressed in experimental COPD, and COPD may be linked to arginine methylation exerted by PRMT activity. Above all, histone methylation may be involved in the pathogenesis of COPD, but the exact mechanism is unclear. Since data on histone methylation in COPD is limited, further *in vitro* and *in vivo* studies are needed to clarify the underlying mechanisms.

Histone Phosphorylation

Histone phosphorylation is believed to play a direct role in mitosis, cell death, DNA repair, replication and recombination[126]. Phosphorylation of histones on serines, threonines and tyrosines, predominantly, but not exclusively, occurs in the N-terminal histone tails[127]. A balance of kinase and phosphatase activities regulates the mitotic phosphorylation of Histone H3 (H3). H3 phosphorylation is mediated by ribosomal S6 kinase (RSK)-2, mitogen- and stress-activated kinase (MSK) -1 and MAPKs depending on the specific stimulation or stress, and thereby induces immediate-early gene expression[128]. H3 phosphorylation at serines 10 and 28 is closely linked to mitotic chromosome condensation and transcriptional activity[129,130]. A role for H3S10 phosphorylation has been demonstrated for the activation of NF-κB-regulated genes[26], which plays a central role in the inflammatory response in COPD[131,132]. Chung et al[76] find that inhibitory kappa B (IκB) kinase alpha (IKKα) activation is critical in phospho-acetylation of H3 on pro-inflammatory gene promoters in response to cigarette smoke stimuli, and the H3 phospho-acetylation is critical for the activation of NF-kB-directed gene expression. In addition, Sundar et al[133] demonstrate that MSK1 is an important downstream kinase involved in cigarette smoke-induced NF-κB activation and phospho-acetylation of H3, which have implications in pathogenesis of COPD. As we know, alveolar macrophages play a critical role in the pathophysiology of COPD by releasing cytokines, chemokines, reactive oxygen species (ROS) and elastolytic enzymes[134,135]. The present study shows an increase in the phosphorylated form of p38 subgroup of MAPKs in alveolar macrophages of smokers with COPD[136]. The p38 MAPK pathway is important in the production of inflammatory cytokines from lung macrophages[137,138]. Moreover, ROS may play a role in enhancing the inflammation through the activation and phosphorylation of MAPKs[139]. Thus, cigarette smoke may induce inflammatory genes expression through histone phosphorylation induced by activated kinases. These kinases may represent potential targets in therapy for controlling cigarette smoke-mediated chronic inflammatory response, including COPD.

Histone Ubiquitination

Recent years, Ubiquitin-Proteasome System(UPS) become a hot topic in COPD. As we know, COPD patients are often accompanied with diaphragm and skeletal muscle dysfunction, which is due to an imbalance between muscle protein synthesis and protein degradation[140-142]. The ATP-dependent UPS is essential for regulating protein degradation[143]. Several reports have confirmed that enhanced protein degradation and atrophy of limb muscles of COPD patient is mediated in part through activation of the UPS[144,145]. The UPS is playing a crucial role in leading to degradation of contractile proteins in COPD, and this system is involved in essential cellular processes such as response to hypoxemia[146,147]. Cigarette smoking can induce skeletal muscle atrophy, which is associate with up-regulation of USP-19 via p38 and ERK MAPKs[148]. It has been found that increased local expression of proinflammatory cytokines triggers the UPS and the loss of myosin in the diaphragm of patients with

mild to moderate COPD[149-152]. In addition, Zou et al[153,154] confirmed that -TrCP (E3-ubiquitin ligase) involves in the pulmonary inflammatory response directly through histone protein O-palmitoylation. Another study showed that CSE treatment can significantly induce the ubiquitination of HDAC2 in epithelial cells, macrophages and mouse lung, causing the reduction of HDAC2 abundance, which is associated with steroid resistance in patients with COPD[36]. Moreover, Kim et al[155] found that CSE exposure can induce Akt protein degradation by the UPS, which plays a critical role in cell survival and proliferation. All these studies indicate that the abnormal activation of UPS plays an important role in the pathogenesis of COPD.

Ubiquitin is a 76 amino acid regulatory protein that is highly conserved in all eukaryotes[156]. Many cellular processes are controlled by the ubiquitination post-translational modification to target proteins, including protein degradation, cell-cycle control, stress response, DNA repair, immune response, signal transduction, transcriptional regulation, endocytosis, and vesicle trafficking[157,158]. The UPS is a well-organized destruction machine with multiple protein components (ubiquitin-activating E1 enzymes, ubiquitin-conjugating E2 enzymes, ubiquitin-protein E3 ligases, and the 26S proteasome) working in concert with one another to ensure the timely and efficient proteolysis of target substrates[159,160]. Ubiquitination of histones plays a critical role in the regulation of several processes within the nucleus, including maintenance of genome stability and transcriptional regulation[161]. This most frequent modification sites has been found on H2A (K119) and H2B (K20 in human and K123 in yeast)[26]. The dominant form of ubiquitinated histones are mono-ubiquitinated H2A (H2Aub) and H2B (H2Bub), a single molecule of ubiquitin added to the highly conserved lysine residues[162]. Mono-ubiquitylation of H2B has been reported to link to transcriptional activation[163, 164]. Ubiquitylation of H2A is important for transcriptional repression[165,166]. Both histones play key roles in genes expression, DNA repair and many other biological processes[167,168]. It has been reported that aberrations of histone ubiquitination or deubiquitination lead to multiple human diseases including cancer[162,169]. However, whether histone ubiquitination contributes to COPD still lack studies and require further investigation.

Conclusions

Cigarette smoke-mediated alterations in DNA methylation and histone modification enzymes and molecules can affect a variety of molecular and cellular processes such as post-translational modifications of histones, gene expression of inflammatory mediators, cell cycle arrest, apoptosis, senescence, autophagy, unfolded protein response, antioxidants or stress response, growth factors, tumor suppressor genes, and DNA replication/recombination/repair[78]. Their role in COPD has become increasingly clear and evidence is accumulating that epigenetic changes may account for some of the heritable effects of cigarette smoking. Knowledge about alterations in DNA methylation and histone modifications will lead to a better understanding of the molecular basis for COPD. However, the molecular mechanisms have not yet been fully understood. These epigenetic changes are potentially reversible and therefore it may lead to the development of novel therapies for the patients with COPD, or methods for blocking the progression of this disease when it is detected in the early stages.

Acknowledgements

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Conflict of Interest

The Authors declare that there are no conflicts of interest.

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