

Mitochondrial Epigenetic Roles in Cigarette Smoke and COPD

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Abstract

Mitochondrial function is important organelle to provide the metabolic necessity to generate and change the epigenetic marks in nucleus reversibly. The Exposure to cigarette smoke (CS) is a significant threat to human health worldwide. Many studies highlighted the role of CS in gene expression, DNA damage, inflammation, and cell senescence. Recently they studied the role of epigenetics and mitochondrial dysfunction in CS and COPD. In this review we summarize the research updated in COPD and CS field related to pathology, pathophysiology, genetic factors, and molecular pathway. Moreover, we separately focus on the mitochondrial and epigenetic and the concept of mitochondrial epigenetic in COPD and CS.

Keywords: *Epigenetic; COPD; Cigarette Smoke; Mitochondria; Histone; Oxidative Stress; ROS; Mitochondrial Epigenetic*

Abbreviations

COPD: Chronic Obstructive Pulmonary Diseases; 5caC: 5-Carboxylcytosine; WHO: World Health Organization; HDAC: Histone Deacetylase; CS: Cigarette Smoke; PTMs: Post-Translational Modifications; ROS: Reactive Oxygen Species; ChIP-seq: Next-Generation Sequencing; mtDNA: Mitochondria DNA; WBC: White Blood Cell; nuDNA: Nuclear Genomic DNA; HAT: Histone Acetyl Transferase; cRNA: Noncoding RNA; GWAS: Genome Wide Associated Study; miRNA: MicroRNA; Acetyl-CoA: Acetyl-Coenzyme; LncRNA: Long Noncoding RNA; DMT: DNA Methyl Transferase; DNMT: DNA Methyltransferase; HMT: Histone Methyl Transferase; ECM: Extracellular Matrix; WES: Whole-Exome Sequencing; CSE: Cigarette Smoke Extract; 5hmC: 5-hydroxymethylcytosine; RNS: Reactive Nitrogen Species; MPO: Myeloperoxidase; NRF2: Nuclear Factor Erythroid Two Related Factors 2; SOD/3: Superoxide Dismutase; NOX: NADPH Oxidase

Introduction

Chronic Obstructive Pulmonary Diseases (COPD), including emphysema and chronic bronchitis, represent 6% of the global mortality rate in 2012, 90% of mortality rate occurs in low and middle-income countries. Based on disease estimation by the World Health Organization (WHO), 65 million people will suffer from moderate to severe COPD by 2030, which will make COPD the third global death caused [1]. COPD developed the aging phenotype gradually due to environmental exposure such as cigarette smoking, and other harmful particles [2]. Several studies have been demonstrated the effect of cigarette smoke (CS) as the leading risk factor for COPD, which is known to be the source of reactive oxygen species (ROS). Besides, these studies have highlighted the role of CS in gene expression, DNA damage, inflammation, and cell senescence. Moreover, some recent studies have highlighted the role of epigenetics and mitochondrial dysfunction in CS. In the last ten years, very few research articles highlighted a combination of mitochondrial dysfunction and epigenetic regulation under

a term called mitochondrial epigenetic. This limitation in mitochondrial epigenetic research articles was because the recent advanced technology may allow performing such research with limited data [3,4].

DNA found in two cellular organelles named the nucleus and mitochondria. Mitochondria contain 16 kb of its genome, and it has essential roles in the cellular response to environmental stress. Mitochondrial dysfunction affects the same genes in Mitochondria DNA (mtDNA) and copied nuclear genomic DNA (nuDNA). This interaction between mtDNA and nuDNA affects the disease severity based on the mutation in copied of mtDNA in nuclear genomic DNA. More evidence has been reported on the association between environmental exposure and mitochondrial dysfunction, such as Oxidative stress and DNA damage [3]. Mitochondria dysfunction refers to cellular events that occur during mitochondrial injuries due to environmental exposure. These cellular events named mitochondrial swelling and shrinkage, the impairment of oxidative phosphorylation, and energy production [5]. However, mitochondrial dysfunction cannot be understood solely without understanding other genetic studies that have a significant impact on disease development and outcomes such as epigenetic [3]. Epigenetic can regulate the gene expression without DNA sequence modification resulting in a change in cellular phenotype and chromatin modification and architecture [3,5]. The epigenetic mechanism can be controlled by noncoding RNA (ncRNA), covalent modifications for DNA and protein such as methylation, acetylation, phosphorylation, sumoylation, ubiquitination, and PARYlation [6].

Epigenetic involvement in DNA methylation, histone modification, microRNA (miRNA), and Long non-coding RNA (LncRNA) can be affected by cigarette smoke (CS), which found to stimulate the inflammatory response and increase the ROS in the lung. The continuous exposure to CS could promote the pathophysiology changes in reaction to COPD and accelerate the risk of developing lung cancer [7].

There are different keys between the mtDNA and nuDNA namely CpG amounts, the lack of retrotransposons in mtDNA, mtDNA methylation, DNA methyltransferase (DNMT) activity, absent of histones complexes in mtDNA, the existence of pre-miRNA and microRNA in mitochondria, and the difference in mtDNA activities based on tissue specificity. Thus, these factors could show how mtDNA depends on the nuclear genome and how mtDNA may regulate the gene expression in the nuclear genome [3-6]. There is growing evidence that epigenetic modification of mitochondrial genome (mitochondrial epigenetic) changes could contribute to COPD. Therefore, this review aims to discuss recent research on COPD development and highlight the evidence of mitochondrial epigenetic communication and dysfunction in COPD.

Chronic obstructive pulmonary disease (COPD): Pathophysiology, pathology, genetic factors, and molecular pathway

Lung tissue contains Alveolus and airway cells. The pathology of Alveolar tissue contains epithelial cells, capillaries, and extracellular matrix (ECM). The membranes contain a complex of elastin and collagen networking proteins. The elastin filaments were generated from tropoelastin monomers that can form into aggregates and fuse with microfilaments. Elastin fibers bind with other proteins such as fibulins, which can link to the ECM component and basement membrane [8] (Figure 1).

The second part is lung tissue called Airway epithelium cells. Airways cells divided into large airways, small airways and Alveolar cells [9]. In a healthy status, Airway cells contain cilia, columnar, secretory, and basal cells. Cilia and columnar cells secrete the mucus and remove the microbes and other particles by clearance mechanism, whereas secretory cells secrete anti-microbial and anti-inflammatory proteins. The basal cells can act as stem cells because they can renew the differentiated cells [8] (Figure 2a). In COPD, Cigarette can cause a loss of cilia cells and change in columnar, which accelerates the secretion of mucus. Moreover, CS led to the loss of Goblet and secretory cells in the small airway, which affect the production of anti-inflammatory proteins and increase the air permeability within the alveolar cell, which grow the difficulties to inhale the oxygen causing the development of COPD later in life [8,10] (Figure 2b).

Due to the limitation in the airway as a result of COPD, abnormal response to inhaling toxic agents may cause the following: (1) chronic mucus hyperplasia (Chronic Bronchitis) due to the chronic cough and phlegm secretion, (2) alveolar destruction and abnormal dilation

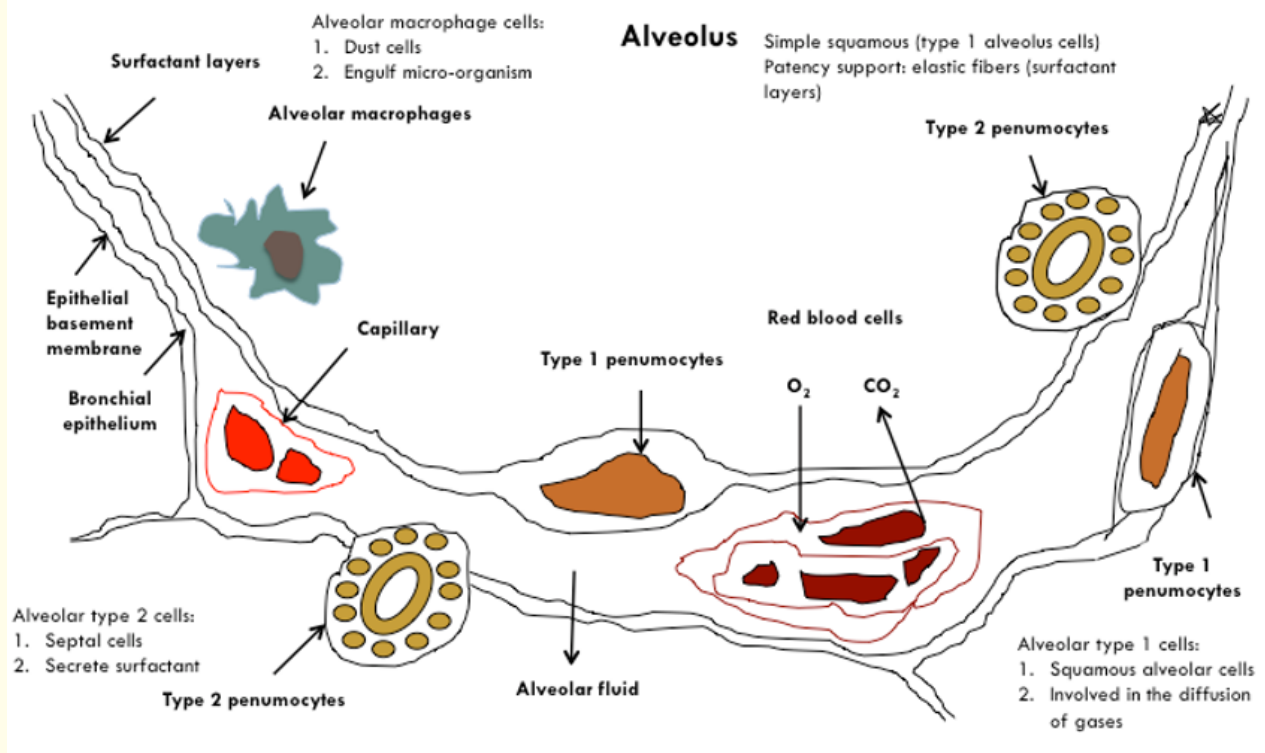


Figure 1: Schematic arrangement of Alveolus in lung tissue represented as a cross-section through a distal airway and alveolar region. The surface of the lung contains different cell types: bronchial epithelium, epithelial basement membrane, and surfactant layers. Each alveolar tissue contains type 1 and types 2, and macrophage cells and Red blood cells and capillary passing through cells.

of airspace (Emphysema) and (3) the disruption of repair and defense mechanism causing inflammation in small airway and fibrosis (Bronchiolitis) [10,11].

The molecular mechanism describes the development, initiation, and progression of the disease. Most of the highlighted signaling pathways showed COPD related to an imbalance in protease and anti-protease, inflammation, oxidative stress, apoptosis, and senescence. These pathways involve in COPD and emphysema.

To start with the recent research in an imbalance in protease and anti-protease compared lung tissue from emphysema patients with normal spirometry and emphysema patients with COPD. The pathological changes under Cigarette smoke extract (CSE) exposure were shown in both groups with changes in the degree of emphysema named the expression of inflammatory factors compared with upregulation in protease due to CSE and downregulation in anti-proteases due to oxidative stress [5]. This observation was shown in studies in neutrophil elastase, which found to cause severe panlobular emphysema and CSE in an animal model [12].

Next, inflammation many of the intracellular and extracellular pathways derived the inflammatory response leading to increase the sensitivity to oxidative stress such as nuclear factor-kb (NF-kB), Ras/Rac, Jun-N-terminal kinase, p38 mitogen-activated protein kinase,

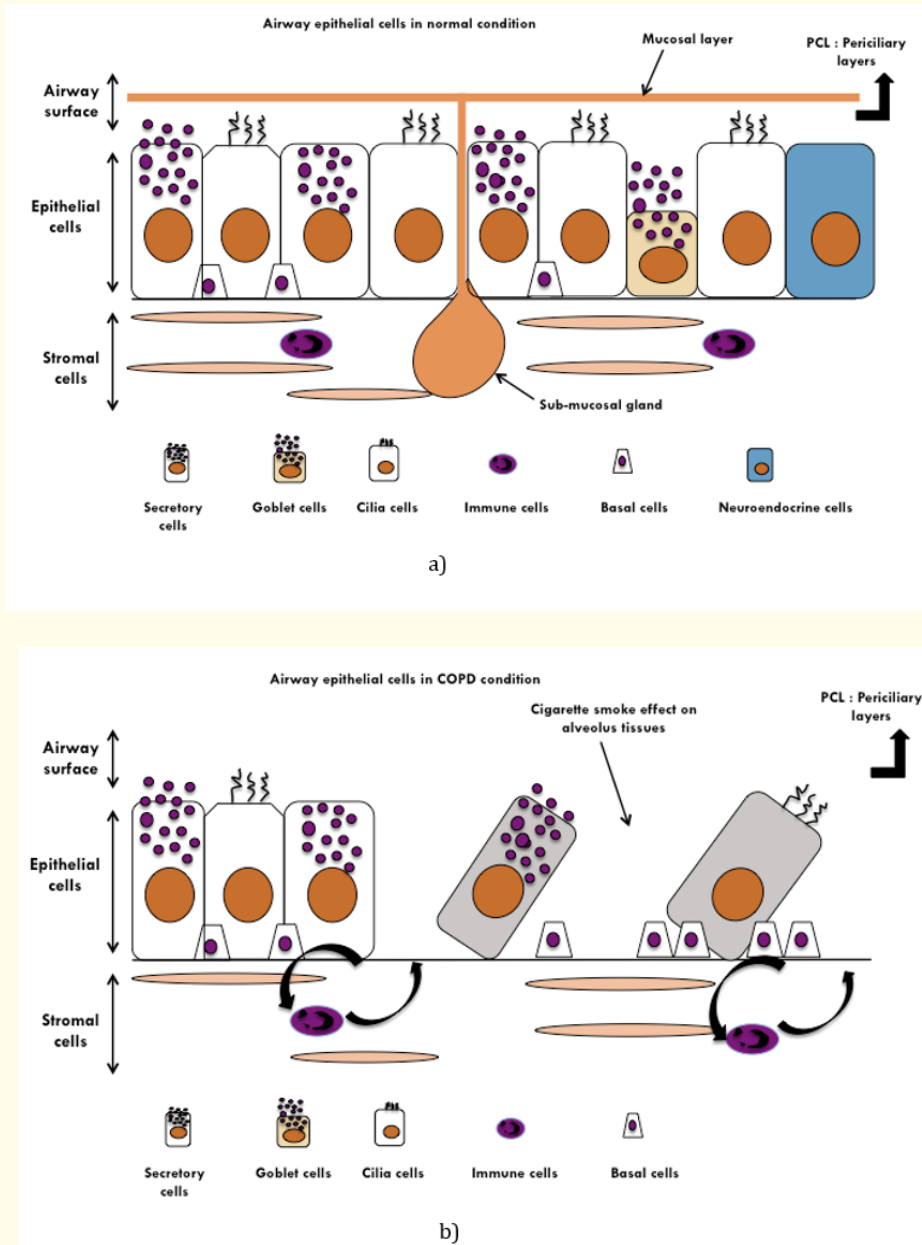


Figure 2: Schematic presentation of the airway epithelium. Airway epithelial defense system in standard (a) and COPD (b) condition cells involved in defense system mechanisms, namely secretory cells, Goblet cells, cilia cells, immune cells, and neuroendocrine cells and basal cells. In COPD, defense mechanisms contribute to chemoattraction and interact with immune cells [55].

and protein tyrosine phosphatase. ROS can act as inflammatory stimuli, which can induce micro-oxidative bursts. Moreover, phagocytosis plays a role in the inflammatory response. COPD is failed to remove the apoptotic cells leading to necrosis and increase COPD inflammation, which activates the oxidative stress and impairs the RhoA intracellularly. However, at the extracellular condition, oxidative/carbonyl stress is caused by tissue protein carboxylation resulting in alveolar macrophage generating a competition at the same pattern recognition receptors (PRRs) [13-16].

Another primary inflammatory cell named Neutrophils can be associated with mucous metaplasia in chronic bronchitis and lung destruction in emphysema. Neutrophils secrete various proteases, namely Neutrophil Elastase (NE), which can degrade the composition of extracellular matrix and play roles in lung destruction in emphysema. A study demonstrated that NE induced the formation of interleukin IL-8, which is enhanced by CSE in human bronchial epithelial cells via PAR2. This PAR2 protein was found to be elevated in lung homogenates and lung epithelial cells from smokers and COPD patients [17].

Environmental exposure such as CS or genetic factors can help to increase the COPD-emphysema pathophysiology, which suggests a role of aging-related mechanisms in emphysema progression. A study highlighted the CS exposure at chronic and sub-chronic level induced by the autophagy dysfunction. They found that the level of ubiquitinated proteins in aggresome-bodies decreased during the treatment with induced autophagy drug. Thus, ubiquitinated proteins level could explain the exposure from CS may weaken the activity of proteasomal and autophagy marker, p62 in aggresome bodies. These activities could change the alveolar pathology and aggresome that may lead to emphysema pathogenesis. Moreover, the reduction in the Sirt1 protein level during the CS exposure suggested that CS mediated the oxidative stress by downregulating the Sirt1 levels to increase the lung again [18].

Around 20% Cigarette smokers developed COPD; thus, Cigarette smoke (CS) is the leading cause of COPD development, increases reactive oxygen species (ROS), and increases the oxidative stress and inflammatory response in COPD patients [19]. Oxidative stress is the disruption of the homeostatic maintenance between antioxidants and oxidants, leading to numerous harmful consequences as a result of eliminating the antioxidants defense mechanism in favor of other agents such as oxidant molecules, carbonyl agents, and biomass fuels. Prolonged exposure to cigarette smoke (CS) results in an airway injury in epithelial cells, causing inflammation in several cell types. As a result of airway inflammation, further damage occurred due to the release of reactive nitrogen species (RNS) and reactive oxygen species (ROS). The term ROS indicates highly unstable species with unpaired electrons such as the free oxygen radicals, hydroxyl radicals, and hydrogen peroxide able to initiate the oxidation mechanism [10-16]. The continuous exposure to oxidant agents generates endogenous and exogenous causes such as a metabolic reaction and cigarette smoke [20,21].

At metabolic status, ROS increases the inflammatory cells into the lung, causing a generation of endogenous ROS. The elevation of oxidative stress directly related to the downregulation of nuclear factor erythroid 2 related factor 2 (NRF2), NADPH oxidase (NOX), myeloperoxidase (MPO) and superoxide dismutase (SOD). ROS is responsible for protein modification and RNA, DNA damage, and mitochondrial dysfunction under reversible and irreversible interaction (Figure 3) [22]. On the other hand, the clinical study identifies that the DNA damage is thorough, measuring the peripheral blood lymphocytes of COPD after three weeks of treatment. A recent study showed that COPD patients have a significant increase in ROS-induced DNA damage after exposure to great exercise without a return to baseline after 4 hours [22]. Moreover, during the rehabilitation, the DNA damage was significantly correlated with pCO_2 , which moderate with acidosis at baseline [22].

Third, apoptosis is known to be associated with COPD. CSE can induce apoptosis in alveolar type 2 cells and anti-apoptosis through sonic hedgehog (Shh). A study in mouse lung epithelial type 2 cells (MLE 12) with CSE could promote apoptosis, whereas Shh, Patched 1 and Gli1 were downregulated in CSE in MLE 12 [23]. Another study showed the role of Forkhead box C1 (Foxc1) in COPD. Foxc1 is a transcription factor and one of the Forkhead box gene family. Moreover, Foxc1 was found to have a role in protecting from oxidative stress and

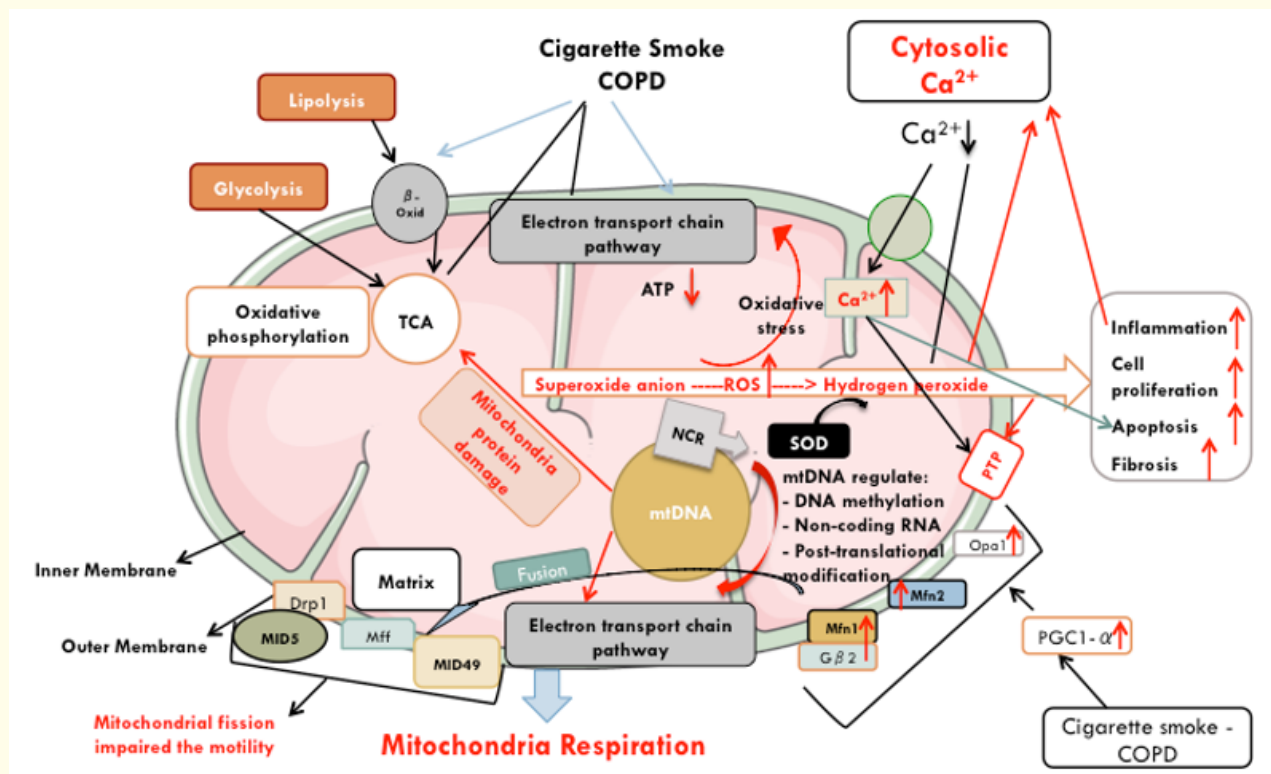


Figure 3: Mitochondria structure and function process during COPD.

apoptosis in eye disease. Similar to eye diseases, Foxc1 overexpression may prevent oxidative stress and apoptosis and cellular inflammation, whereas knockdown in Foxc1 showed the opposite [24].

Cell senescence can be affected by the CSE, which can accelerate aging, causing a rapid decline in lung function. Consequently, the loss of Alveolar cells functions to renew and repair itself lead to the initiation of lung deteriorating, then emphysema development. A recent study on coactivator called coactivator associated arginine methyltransferase-1 (CARM1) found to play a role in airway repair and regenerating by regulating airway epithelial cell senescence [25]. Another study on 27-hydroxycholesterol (27-OHC) which is an oxysterol produced by oxidation reaction of cholesterol by sterol 27-hydroxylase. The research found that 27-OHC increase the cellular senescence in lung cells [26].

In the lung, there are specific signaling pathways involved in lung development named Wnt/ β -catenin, Notch, Bone morphogenic protein, hedgehog, and retinoic acid pathways. Wnt/ β -catenin, in the context of lung injury and repair, was shown to increase the proliferation of lung epithelial cells. In COPD, a transcription factor named nuclear factor erythroid-2-related factor-2 (Nrf2), which can protect the cells against oxidative stress through the expression induction of anti-oxidative genes, found to be the mediator between Wnt3a/ β -catenin and an activator of Nrf2 called AMP-activated protein kinase (AMPK) [27]. Another study found that miRNA (miR-130a) inhibition triggers the cell injury treated with CSE, and miR-130a overexpression regulates the Wnt/ β -catenin via aggravates the Wnt1. This study may indicate a therapeutic target for COPD induced by CSE [28].

The Notch Signaling Pathway (Notch) plays a critical role in cell-cell communication. In COPD, the research found a down-regulation on Notch key components (Notch1, 3, 4 and target gene Hes1 and Hes2). In contrast, the expression increased in Notch 2 and extracellular signal-regulated kinase (ERK) 1/2 in COPD patients. Moreover, overexpression of Notch 1 mitigates the cell apoptosis in cells with CSE treatment. These results indicate that CS can change the Notch signaling in lung endothelial cells, and Notch 1 used as a protector against apoptosis in cells treated with CSE via activating the ERK signaling, which regulates the methylated promoter of mitochondrial transcription factor A (mtTFA) [29]. Similar results found Notch 1 and Multidrug resistance-associated protein-1 (MRP1) found to have a protective effect in COPD [30].

Bone morphogenetic protein (BMP), specifically BMP-4, affects the epithelial progenitor cells during the development of adult mouse lung. BMP-4, which is a secreted transforming growth factor- β family member, found to be upregulated in airway epithelium in COPD smokers. In Airway basal stem/progenitor cells, the increase of BMP-4 showed promotion in changing the phenotype of these airway progenitor cells [31].

Hedgehog (hh) canonical type refers to the activation pathway through binding ligand called Shh, Dhh and Ihh to its receptor Ptch. This binding leads to the release of the Smo receptor and changes the activity of the Gli transcription factor family. The non-canonical type has three modalities: ligand-dependent/Smo-independent activation, ligand-dependent/Gli-independent activation, and Gli-only activation. Hedgehog (Hh) signaling plays a vital role in airway epithelium in COPD patients by maintaining the balance between proliferation and quiescence during homeostasis and regeneration. Thus, the Hedgehog (Hh) pathway activity is essential to establish functional airway epithelium. Moreover, Gli 2 found to be responsible for lack of cilia cells during the hedgehog pathway inhibition, and Gli 2 with receptor Smo activation are the key marker for COPD development [32].

Retinoic acid (RA) and its receptor have a role in lung formation and COPD. Retinoid X receptors (RXRs) are nuclear receptor (NR) that regulates the gene transcription, and it acts as homodimers or heterodimers with receptor peroxisome proliferator-activated (PPAR) and liver X receptors in the lung. Retinoid X receptors (RXRs) could be used as therapeutic potential [33].

Genetic factors play essential roles in COPD. There are several gene mutations involve as matrix and have a strong correlation with emphysema, namely ELN, FBLN4, FBLN5, FBN1, ATP7A, TGFB1 and LTBP4. Then, there are several mutations involve as anti-protease, namely SERPINA1, SERPINE2, and TIMP2, whereas others involve in modification as protease enzymes such as MMP1, MMP9, and MMP12. In addition, mutated genes affect as detoxification such as GST-P1, GST-M1, HMOX1, SOD3 and another mutated gene affect as inflammation such as TNF and GC [34].

Genome wide associated study (GWAS) showed that protein IREB2 found on chromosome loci 15q25.1 might affect the regulation of iron hemostasis in COPD [35-37]. The gene body of FAM13A has a strong association with COPD in human, whereas *Fam13a* in murine showed a mild effect of promoting COPD could be a result of regulating the degradation in B-catenin, which is essential for alveolar epithelial cell repair and regeneration. Moreover, researchers found that knockout mice *Fam13a* showed a smoking resistance and increased the level of β -catenin in the lung, whereas unknown this condition in human [38]. Another gene that genetically induced emphysema named SERPINA1, which is a mutation, occurs in an alpha-antitrypsin gene. This mutation showed an increase in protein modification to form dysfunctional polymers for inhibiting the target enzyme, neutrophil elastase [34].

The loci of COPD and lung function in the general population showed a substantial overlap correlation in these loci, including the non-smokers. GWAS showed that COPD patients have a reduced lung function at an earlier age. Moreover, gene enrichments were expressed differently during lung development in COPD. These genetic loci showed enrichment in the regulatory region of the fetal lung, which highlights the role of embryonic development pathway in early prediction for COPD [39].

Genetic factors play a role in COPD susceptibility. A recent study demonstrated the genetic risk of COPD using GWAS of 35,735 cases and 222,076 controls. Based on genes, cell types, and biological pathways in this study, it was seen that the genetic basis for clinical heterogeneity in COPD. The data supported the previous role for real-life events in the risk of COPD and confirmed the enrichments of heritability for epigenomic marks in fetal lung. The epidemiological studies showed that the risk of COPD might develop in early life based on genetic variants from primary lung function. To test these genetic variants at the early stage of the lung, the induced pluripotent stem cell (iPSC) model derived from alveolar type 2 lung cells could help experimentally to answer the role of these genes in early life [40].

GWAS on COPD confirmed previous studies that the risk of COPD might develop in early life and genetic variants may set initial lung function and patterns of growth [41]. There are second-degree indirect interaction COPD diseases; these pathways are not related to lung development, including mesenchyme development and extracellular matrix, cilia structure, elastin-associated microfibrils, and retinoic acid receptor beta. GWAS, moreover, found novel genes named ADAMTSL3, which play an essential role in cell-matrix interactions, and the CHIA gene, which is associated with chitinase acidic and exhibit lung-specific expression in asthma [41].

Moreover, COPD is associated with bone destruction in inflammatory disease. Osteoporosis in COPD patients found to be around 35.1%. One of these studies highlighted the role of Interleukin (IL)-17 (IL-17A) in COPD patients since the researchers found that an increase in the expression of IL-17A in COPD and a general decline in lung function. The results showed that IL-17A linked to bone loss induced by long-term exposure to CS in the mouse model of COPD. IL-17A results could be through the pro-inflammatory effects and up-regulation of RANKL expression in bone tissues [42]. GWAS analysis found that Hedgehog interacting protein (HHIP) at locus 4q31 and protein patched homolog 1 (PTCH1) genes were identified close to as COPD susceptibility loci. On the other side, this region associated with lung function reserved in the general population. The COPD susceptible variant in HHIP locus identified within the distal enhancer, which controls the expression of HHIP via chromatin interaction [39].

The microbiome varies with exposure to different environmental factors, and tobacco smoke inhalation has been shown to induce pathological changes to the integrity of the airway epithelial barrier and cell-cell contact via the degradation of tight junction proteins, inducing cilia autophagy, goblet cell hyperplasia and an increase in epithelial permeability [43-47]. Cd is a heavy metal and environmental pollutant, causing oxidative stress and toxicity in animals and humans. Food is the primary source of Cd for the general population, while occupational exposure and/or smoking tobacco leads to high levels of Cd accumulation. While information is readily available for toxic mechanisms of Cd for acute and high-dose exposures of occupational and smoking exposures, limited numbers of studies on low dietary levels of Cd have been conducted [46].

Aging in COPD

Aging defines a progressive decline in homeostasis. With a repeated infection of the lung during the increase of age, the pulmonary function declined. Nine hallmarks help to increase aging found in COPD, namely: 1) genomic instability, 2) telomere attrition, 3) loss of proteostasis, 4) deregulated nutrient sensing, 5) cellular senescence, 6) stem cell exhaustion, and 7) altered intercellular communication [47]. Two other hallmarks that affect the aging in COPD are 8) epigenetic alteration and 9) mitochondrial dysfunction. These two will focus on later in the article.

The oxidative damage in nuclear DNA is caused by ROS, such as base mutation, strand break, DNA-protein cross-links, and the formation of DNA-adducts. ROS generated hydroxyl radicals, and they could interact with DNA bases, sugar-phosphate backbone, and deoxyribose moiety. ROS product results lead to a significant mutation in DNA bases and DNA single or double break generating other risk factors such as genomic instability, cell cycle disruption, and cell death. Besides, hydroxyl radicals induced the DNA-protein cross-links, which involve in thymine and tyrosine of histone and DNA. Moreover, ROS induce the other macromolecules reacting with deoxyguanosine and deoxyadenosine formed DNA adducts such as aldehyde activation created in lipid peroxidation [48-51]. Studies showed that cell senes-

cence is a result of telomere shortening, DNA damage, and high concentration of ROS. Alveolar epithelial and fibroblast senescence found COPD, which showed an inflammatory imbalance and repair process results in a structural modification in the peripheral airway and lung parenchyma [50].

A study on both genomic and functional approaches on the lung for a smoker with COPD in human showed an accumulation in DNA damage and an increase in γ H2AX related to smokers without COPD. *In-vivo* study on mouse identified the ATM/p53/p21 involve in the development of CS-induced emphysema. Recently, researchers found transforming acidic coiled-coil-containing protein 2 (TACC2) as a COPD gene using whole-exome sequencing (WES). TACC2 found to be in 8 from 62 COPD patients opposite from non-smokers. Moreover, applying the TACC2 siRNA showed an enhancement in CS-induced apoptotic cell death in human broncho-epithelial cells (HBECS) and suppresses HR repair. However, TACC2 overexpression can reduce the effect of CSE on DNA damage and cytotoxicity [51]. In human, the apoptotic cell numbers used as evidence for TUNEL positivity and caspase-3 activation in alveolar septal cells is increased in smokers with COPD as compared with smokers without COPD [51].

Telomeres contain a sequence of repetitive hexanucleotides that protect the end of chromosomes from being recognized as double-strand breaks and truncation. The lack of DNA ability to duplicate the end of chromosome results shortening in the chromosome. Therefore, telomeres during cell division progress shortly, which indicates the replication termination process [52]. In COPD cases, the loss of telomeres due to oxidative stress as a result of DNA damage [52]. A study on 422 patients found that COPD patients have shorter telomere than smokers; however, they found no relation between telomere alteration and lung function clinically, making the telomere length challenging to apply as a possible biomarker for COPD progression [52]. The enhancement of Telomere attrition found in small airway epithelium from COPD patients, which could explain the susceptibility to inflammation due to genetic factors [53].

Proteostasis is part of the metabolism process that represents the lung cell proteins, including protein synthesis, folding, transportation, functions, aggregation, and degradation [54-56]. Chaperons such as heat shock proteins play essential roles in aging and aging-related to disease. It showed that they are upregulated with aging to maintain proteostasis, such as HSP70 in mice [47]. Cells can recognize and respond to fuel sources, using nutrients sensing. Deregulation condition in nutrient sensing occurs when an integration signal on available nutrients can regulate cell growth. This case involves a cellular pathway named PI3K-AKT-mTOR, which has an essential pathway in cellular senescence and again [57].

In CS Overexpression in SIRT1, which is part of the Sirtuins family, a nicotinamide adenine dinucleotide (NAD) depends on protein deacetylases and ADP-ribosyltransferase1. NAD (Sirtuins) family, considered as anti-aging molecules, showed downregulation of senescence-associated genes LncRNA1, SIRT1/p53, FOXO3 in lung tissue in COPD patients. SIRT1 effects could indicate a significant role of LncRNA1 in the pathogenesis of COPD [47]. A recent study used tissue-resident mesenchymal stem cells (LR-MSc) from healthy lung as an essential regulator for inflammatory response. Moreover, the study showed that the location of LR-MSc was in the endothelium. COPD under current smoking status showed impairment in the immune capacity of T CD8 with a link to different cytokines expression levels, whereas this observation did not demonstrate in the smoker with healthy lung or COPD with ex-smoker status. LR-MSc cells were exposed to SC extract showed downregulation in the capacity of the immune system [60]. Inflammation is the way that cells can communicate with each other. Aging is involved in alteration in intercellular communication such as endocrine, neuroendocrine, and neuronal signaling. Increasing the level of Pro-inflammatory cytokines by senescent cells and dysfunction in the immune system is associated with aging, which is associated with chronic low-grade inflammation [61].

Mitochondrial dysfunction in COPD

In mammals, Mitochondria contain 16.569 kb of circular double-strand DNA, and they have 37 genes. These genes under the control of nuDNA and mtDNA, and 24 of those genes involved in mitochondria translation named two ribosomal (rRNA) and 22 transfer (tRNA).

The rest of mtDNA genes are encoded subunit in respiratory complex I, III, and IV unlike complex II are encoded by nuclear genes [62-65] (Table 1).

mtDNA genes	mtDNA proteins	mtDNA function	COPD
MT-ND1	NADH dehydrogenase (Complex I)	Create an electrochemical gradient across the inner mitochondrial membrane from NADH+H derived from nutrients	Increased
MT-ND2			
MT-ND3			
MT-ND4			
MT-ND4L			
MT-ND5			
MT-ND6			
MT-CYB	Coenzyme Q-cytochrome C reductase (Complex III)	Produce small amounts of ROS Transfers electrons through the Q- cycle	Increased
MT-CO1	Cytochrome c oxidase (Complex IV)	Providing the complete reduction of O ₂ and minimizing the production of ROS.	Increased
MT-CO2			
MT-CO3			
MT-ATP6	ATP synthase	Transferring the energy from inner to intermembrane requires ATP synthase	Increased
MT-ATP8			
MT-TA	Transfer RNA (tRNA)	Assemble protein building blocks (amino acids) into functioning proteins	Mistranslating the tRNAs
MT-TR			
MT-TN			
MT-TD			
MT-TC			
MT-TE			
MT-TQ			
MT-TG			
MT-TH			
MT-TI			
MT-TL1			
MT-TL2			
MT-TK			
MT-TM			
MT-TF			
MT-TP			
MT-TS1			
MT-TS2			
MT-TT			
MT-TW			
MT-TY			
MT-TV			
MT-RNR1(12S)	Ribosome RNA (rRNA)	Functions as a riboprotein for translating mitochondrial mRNAs encoded in mtDNA	Decreased due to DNA methylation
MT-RNR2(16S)			

Table 1: The mitochondrial genes and function.

Mitochondrial dysfunction may lead to stress, which causes an imbalance in homeostasis mechanisms named biogenesis, fusion/fission, and mitophagy. Biogenesis generates from the growth and division of pre-existing mitochondria, and it was becoming activated as a response to stress. The transcriptional regulation in biogenesis occurs through the coordination of nuclear and mitochondrial encoded proteins with a response to nutrient modification. In addition to the regulation, a mitochondrial transcriptional factor included such as PPAR coactivator (PGC-1), A (TFAM), AMPK, and NRF1/2 [66,67]. In the lung, biogenesis occurs at the following: the Alveolar type II cells from distal lung cells, small blood vessels and inflammatory region of alveolar [66]. In COPD, the biogenesis process depleted, which may link to the loss of nutrients and muscle mass [66].

Mitochondrial fission/fusion allows the mitochondrial to maintain the healthy condition or OXPHOS, and it is associated with for formation of new mitochondria. In Fusion, the outer mitochondrial membrane contains a protein called GTPases mito-fusion 1 and 2 (MFN1/2) and inner membrane protein called optic atrophy 1 (OPA1) mediates the fusion process. The fission process needs activation of dynamic-related protein 1 (DRP1) from the cytosol to receptors (fission protein 1, fission factor; and elongation factor 1 and 2) [54]. If the fusion process increased or the fission process decreased, it promotes the formation of an elongated mitochondria network. On the opposite side, high fission and low fusion lead to fragmentation in mitochondria [66,67]. The increase in fission and fusion indicates COPD and lung cancer, whereas the decrease in the fusion process highlighted in lung cancer [67].

Damaged mitochondria are removed and marked for degradation to reduce the electrochemical gradient, $\Delta \Psi$, that is translocation depends on a protein called PTEN-induced kinase 1 (PINK1) between outer and inner membrane. PINK1 protein activation will lead to mitochondrial arrest and hold in mitophagy. Therefore, this action will help to maintain the healthy function of mitochondria. CS can induce the phosphorylation of dynamin-related protein 1 (DRP1), which is an essential step toward the fragmentation in mitochondria by increasing the mitophagy and cellular necroptosis processes [67]. Stress condition in the lung with CS increased the respiration system in mitochondria; then, it will activate the mitophagy and lead to necroptosis in lung epithelial cells and emphysema [66,67] (Figure 3).

The nature of mtDNA has a lack of any protection for its DNA, such as histones; thus, mtDNA is may be a target for ROS [62]. At the protein level, respiratory complexes contain 92 proteins, and a minimal amount of 92 are mitochondrial-encoded protein, and the majority of these proteins encoded in the nuclear [66-68]. In healthy cells, Mitochondria contain 2-10 copies of their genome. In COPD patients, it was found that leukocytes have a lower number of mitochondria and lower glutathione levels in comparison with smokers and non-smokers patients. Moreover, airway smooth muscle (ASM) cells in COPD showed damage and an increase in mitochondria ROS, such as mitochondria-specific antioxidants (MitoQ) and decrease cytokine secretion and ASM proliferation comparing with healthy cells. Next, the bronchial epithelial cells in COPD showed fragments in mitochondria and the production of mitochondria ROS induced by CS, leading to cellular senescence [69]. Dysfunction in mitochondria can interact in aging through CS impairment in cellular respiratory activity and mitophagy. This interaction could increase ROS, induce cellular senescence, and released molecular patterns named SIRT3 and telomere due to the accumulation of mitochondria damage [57,61]. AITC upregulated the expression of MRP1 and attenuated oxidative stress and GSH-redox dysregulation in COPD through Nrf2 and Notch1 signaling pathways [70]. Significant sex differences in urine mitochondria DNA (u-mtDNA) levels were observed, with females having higher u-mtDNA levels across all study subgroups. U-mtDNA associated with worse spirometry and CT emphysema in males only and worse respiratory symptoms in females only. Similar associations were not found with Urine albumin/creatinine ratios (UACR) [72-74].

Epigenetic changes in COPD

Epigenetic marks, namely DNA methylation, histone modification, non-coding RNA, play an important role in chromatin modification and function. DNA methylation is the result of the methyl group bind to cytosine residues in the covalent bond. This bind is part of cytosine-guanine (CpG) dinucleotide located at the promoter area of each gene, causing repression in the transcriptional process of the target gene called gene-silencing process [46]. Most of DNA methylation in mammals found as 5-methylcytosine (5mC) at CpG Island in the pro-

moter region of the gene. Other form of DNA methylation named 5-hydroxymethylcytosine (5hmC), 5-formylcytosine (5fC), and 5-carboxylcytosine (5caC) [76]. The pathway of DNA demethylation can be impaired by oxidative stress resulting in two products: 8-Oxoguanine (8-oxoG) as an outcome of guanine oxidation [76] and the oxidation reaction of 5mC to 5hmC [76]. A unique study firstly highlighted the genome-wide methylation data [76]. This data was on the DNA modification with 5mC and 5hmC separately, and gene expression in alveolar macrophage enriched with bronchoalveolar lavage cells from healthy smokers and non-smokers. The results showed a large number of smoking associated with differentially methylated positions (DMPs). Cells with 5mC and cells with both 5mC and 5hmC were hypomethylated, whereas 5hmC cells were hypermethylated, and many of these expressions associated with enhancers based on a database called FANTOM5. Thus, this study supports the hypothesis that oxidative stress is smoking associated, causing the demethylation in DNA through a repetitive oxidation process of 5hmC as a first step [76]. In addition, tobacco smoke exposure epigenetically modifies BAL cells, possibly involving continuous active demethylation and subsequent increased activity of inflammatory processes in the lungs [77-91].

Many studies focused on DNA methylation regulation in CS. The results from the different sample size, races and areas indicated that changing the DNA methylation at CpG sites are stimulated by the CS leading to changing in gene regulation reversibly and more vulnerability to COPD [92]. Based on research, The Global reduction of DNA methylation showed a link with aging, and the number of methylated genes could be used as a predictor for human aging [47]. In COPD patients, Hypermethylation was reported on the study identified gene components of the PI3K/Akt and Nrf2 pathways [46]. Similar to this study, hypermethylation was observed in the correlation between PTEN and Nrf2 genes under expression reduction of gene products [46].

Chromatin is a dynamic structure that can regulate all processes involving DNA, which include DNA synthesis, transcription, translation, DNA repair, and recombination [93]. Many factors are known to affect chromatin compaction and dynamics, including histone variants, non-histone architectural proteins, histone chaperones, heterochromatin factors, and chromatin-modifying enzymes, linker histones, and chromatin remodeling factors [94]. Post-translational modifications (PTMs), histone chaperones, and ATP dependent chromatin remodelers can all regulate nucleosome stability, dynamics, and structure. PTMs can change the histone's tails enzymatically by adding or removing marks such as methylation, phosphorylation, acetylation, ubiquitylation, and ADP-ribosylation [95]. In environmental effects, Histone modifying enzymes guide the DNA methylation and histone modification to respond to these effects such as cigarette smoke (CS). Thus the chromatin modification is linked to inflammation, immune response, oxidative stress, and antioxidant genes. Gene expression Study on human bronchial epithelial cells (H292) and mouse lungs found that a high increase in the expression of chromatin enzymes named DMT, HAT, HMT, and SET proteins, histone kinase and ubiquitinase [96,97]. Moreover, histone modification called H3K56ac and H3K12ac found to be induced by CS and damage response, which affects the transcription of the target gene due to the different influences from genotoxic stress [98,99].

Another study was on CS exposure for the different duration (3 hours, two days, and four days) in human bronchial epithelial (HBE) cells cultured in an air-liquid interface, which is 3D model can recapitulate sub-chronic CS exposure in HBE cells. In addition, the analysis was from a genome-wide enrichment study following by next-generation sequencing (ChIP-seq). The results indicated that H3K27ac was detected on HBE cells with changes in its expression during the time point. This observation showed series of Transcriptional factors induced by CS found to have H3K27ac enriched at their loci named: B-myb binding sites, which related to immortalized endocervical cells, E2F, which may be related to pulmonary artery involved in COPD patients, and the binding of Egr-1 and E2F which found to regulate the autophagy gene LC2B by HDAC reduction previously observed in emphysema [98].

Histone modifications, DNA modifications, and histone variants interact with each other to regulate chromatin activity. For instance, the interaction between DNA methylation and H3K4me can inhibit the methylation at CpG islands in the embryo [95]. This interaction has been referred to as an "epigenetic code" that affects chromatin structure and transcriptional activities. Chromatins modifications are affected by proteins that can write read and erase these chromatin marks to promote or inhibit their roles in the cells such as DNA repair;

chromosome condensation, and cellular reprogramming [99]. On the other hand, writers can add histone modification such as acetyl and methyltransferase, kinase, and ubiquitinase, whereas eraser enzymes remove those histone modifications, such as deacetylase, phosphatase, demethylase, and deubiquitinase. These recognized domains of readers and writers are located in different protein complexes, catalytic domains, and scaffolding domains [100] (Figure 4).

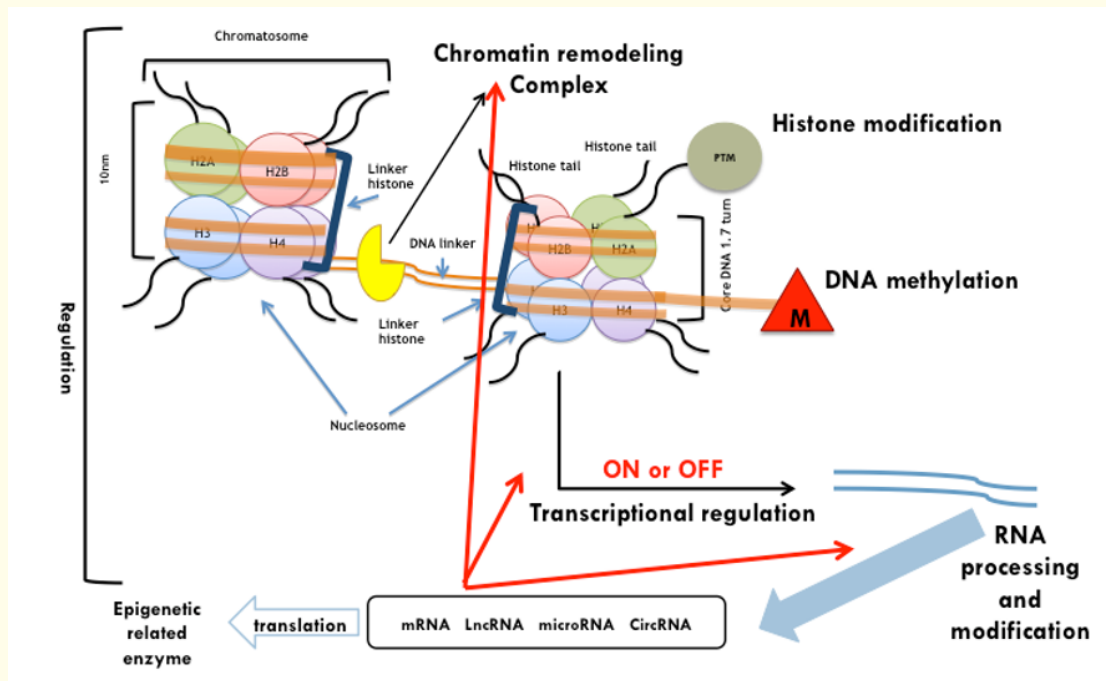


Figure 4: General schematics of chromatin structure underpinning COPD. Chromatin is regulated by DNA methylation, histone post-transcriptional modifications (PTMs), and chromatin remodelers. These chromatin modifications act coordinately to control RNA transcription. On transcription, RNA processing and modifications add another layer of control on protein synthesis. The RNA products, including long noncoding RNAs (lncRNAs), microRNAs, and circular RNAs (circRNAs), in turn regulate chromatin remodeling, gene transcription, and mRNA processing and modifications. Notably, epigenetic modifications also regulate the expression of epigenetic players, such as epigenetic-related enzymes, which in turn modulate the 3D architecture of chromatin. Schematic representation of chromatin where the nucleosomes (blue arrows) are formed from 1.7 turn of DNA (orange threads) wrapped around two-histones octamer. H2A, H2B, H3, and H4 octamers formed two subunits of each H2A (Green ball), H2B (red ball), H3 (blue ball), and H4 (purple ball). Linker histone (H1) the (dark blue bracket) located between DNA and octamers and linker DNA located between nucleosome. Each octamer subunit has histone tail (black thread) that can be modified by methylation, ubiquitination, phosphorylation, or acetylation.

Moreover, Histone modifications affect the histone-DNA complex and gene regulation in aging in COPD. DNA methylation in alveolar cells in COPD patients affects many genes related to COPD pathway, lung function, and aging, such as Oxidative response signaling pathway called nuclear factor erythroid 2-related factor 2 (Nrf2) and aryl-hydrocarbon receptor repressor gene (AHRR). Furthermore, histone deacetylase (HDAC) reported being a negative regulator for pro-inflammatory cytokines in COPD. The activity of HDAC in lung tis-

sues decreased at the same time, the interleukin (IL-8) mRNA is increased with an increase in the COPD severity in patients [47]. Another study found the negative relation between HDAC2 expression and pro-inflammatory CD28 null CD8+ cells and positive relation with FEV1 in COPD patients. Nrf2 showed instability due to the downregulation of HDAC2, leading to a reduction in the synthesis of anti-oxidant molecules and an increase in the cells' susceptibility toward oxidative stress during CS exposure [47].

Non-coding RNAs such as mRNA, miRNA, LncRNA, and CircRNA play important role in protein regulation. MiRNA can repress the protein expression through targeting the mRNA degradation by binding to 3'-untranslated region (3'-UTR) in sequence specific. Researcher found that miR-181c was decreased in lung tissue in human and mouse with COPD comparing with non-smokers. This observation was shown in inflammatory response, neutrophils, ROS and inflammatory cytokines. Researchers found a direct interaction between miRNA-181c and CNN1, which is a prototypic members of (CCN2 (CTGF), CCN1 (CYR61), and (CCN3 (NOV)) and it contains a high conserved cysteine rich structure. The protein family play important role in cellular processes such as growth proliferation and regulation, adhesion, migration and angiogenesis [101,102]. Moreover, miR-126 (miR-126-3p), which is highly expressed in endothelial cells and it play important role in angiogenesis and vascular homeostasis, was downregulated in COPD patients. This downregulation results an increase in DNA damage response and repressing the ATM protein kinase activity as response to pathophysiology of COPD [103]. A another study conduct the different type of small RNAs in human plasma derived extracellular vesicles as circulating biomarkers in smokers and COPD patients comparing with non-smokers using small RNA-sequencing as comprehensive analysis. This study used cell-derived extracellular vesicles (EV)/exosome mediated cell-to-cell communication and immunoregulatory functions and recently used as circulating biomarkers. (EV)/exosome in this study contains high amount of surface markers, histocompatibility complex, regulatory proteins, mRNA and miRNA and this exosome enriched in biofluids such as serum, plasma and blood, bronchoalveolar lavage, saliva and urine. The results of this study found 45 miRNA were differently expressed for non-smokers and COPD. One of these miRNA named miR-335-5p was downregulated and associated with 12 target genes that involved in cytokines signaling, MAPK, JNK and angiogenesis [104].

Another non-coding RNA called long non-coding RNA (LncRNA) has 200 nucleotides and it classified into sense, antisense, bidirectional, intronic, and intergenic lncRNAs. Although there is a growing focus on LncRNA roles in the pathology of the diseases, it remain less or lack of published works of LncRNA in lung diseases and the use of exosomal LncRNA in lung diseases which could help to understand the lung development [105]. A study used two different analysis called gene ontology (GO) and Kyoto encyclopedia of genes and genomes (KEGG) to identify the lncRNA expression genes that where mainly involved significantly alter the pathway of endoplasmic reticulum and taurine and hypotaurine metabolism pathway in cigarette smoke induced COPD mouse model [106].

Circular RNA (circRNA) is a member of non-coding RNA, which originated from pre-mRNA stemmed from the splicing process. CircRNA are more stable because it forms a closed loop structure. A study on human small airway epithelial cells showed 4,384 from total 10,738 around 41% of circRNA genes were expressed in smoking groups; these smoking group found a reduction in the biogenesis of circRNA. 65-circRNA expressions were unregulated whereas 100 of circRNA expression were downregulated in smoking groups [107]. One of circRNA named hsa_circ_0016070 besides mir-R-942 and CCND1 in pulmonary arterial hypertension (PAH) associated with COPD using microarray analysis results. In addition, hsa_circ_0016070 reduced the miR-942 level and its associated gene CCND1 expression in PAH with COPD patients [108].

Mitochondrial epigenetic in COPD

The concept of mitochondrial epigenetic relied on the communication that involved histone modifications proteins and epigenetic marks. This concept represents in several biological facts that were highlighted by many research studies. Firstly, body metabolism and physiological response regulation need epigenetic and its process. Second, Mitochondria are the generative master of energy to supply most cellular functions with ATP via the OXPHOS pathway. Third, Mitochondria hold the fatty acid oxidation pathway as the primary source of acetyl-coenzyme (acetyl-CoA), which is also crucial for epigenetic modification. Next, the mitochondrial genome inherited from

single-sided maternal, and it has 13 encoded genes, whereas the nuclear genome inherited from both parents, including the mitochondrial proteins and enzymes [109-112].

However, this communication could be more complicated than what has already been represented because of the number of copies of mitochondria per cell, the high mutation rate in mitochondria, then the nuclear genome, and the heteroplasmy and connection between nuclear and mitochondrial genome during diseases [112-115]. To address these complex, white blood cell (WBC) count is considered a marker for inflammatory response. The negative correlation between WBC count and mtDNA copy number indicates a change in mitochondria biogenesis during the immune response. In COPD, it found that reduced the number of WBC was associated with decreased leukocytes mtDNA copy number. However, due to the different immune cells in the WBC and all the immune cells undergo similar age-related changes in mtDNA copy number, it may be involved in the mtDNA copy number reduction [113]. Moreover, a study highlighted the mtDNA mutation and mtDNA heteroplasmy in smoker patients with an HIV-positive infection between ages 2 - 72 years old. The study found that a positive relationship between age and the presence of heteroplasmic point mutation and mtDNA heteroplasmy was increased in the parotid gland and buccal cells of tobacco smokers. The effect of smoking on mtDNA heteroplasmy apposing the lack of effect on somatic mtDNA substitute suggested a smoking influence on cells shared the same mutations rather than a new generation of mutation [114].

The communication between mitochondria and nucleus through epigenetic markers

Some nuclear DNA factors regulate mtDNA molecular mechanisms such as replication, transcription, and nuclear-encoded RNA from the nucleus to mitochondria [115]. There are several factors are involved in the communication between mitochondria and nucleus named: Acetyl-CoA, orotic acid, α -ketoglutarate (α -KG), 2-HG, Fumarate, Succinate, ROS, SAM, Sirtuins, TET, JMJDs, LSDs, FAD, NAD, ATP, kinase, DNMT, HMT, HATs, and HDACs (Figure 5). These factors involved molecular pathways in mitochondria and/or nucleus named, TCA cycle, pyrimidine synthesis, cytosol citrate synthesis, methionine synthesis, OXPHOS pathway, NAD salvage pathway, DNA methylation, Histone methylation, and Histone acetylation, and NcrRNA transportation system and roles between mitochondrial DNA and nucleus. To start with, Orotic acid is the building block of pyrimidine synthesis and generates in the electron transport chain [115]. A research study found that orotic acid was high in breastfeeding cigarette smoke (CS) mother due to the possible deficiency in arginine, orotic aciduria [116].

Second, at metabolic status, the impact of ROS on nuDNA is high, and it can damage the nuDNA at a different level. This impact leads to metabolic alteration in mitochondria resulting in an accumulation of many intermediates between nuclear DNA and epigenetic factors [115]. ROS typically released in the mitochondria, which involved in the production of energy (ATP), whereas increasing ROS due to oxidative stress can damage the mitochondria, which becomes vulnerable to stress than nuclear DNA damage and show to modify the nuclear DNA methylation. Recent work showed that oxidative stress could occur through the effect of air pollution on mtDNA methylation [3]. Mitochondrial genome found to lack retrotransposons such as LINE-1 and *Alus* that compromise 40% of the human nuclear genome (nuDNA).

Furthermore, mtDNA was less methylated than nuclear DNA; however, the activity DNMT could be used to distinguish from other cellular DNMT. Next, mtDNA methylation is more controversial than genomic DNA methylation. In addition, histone complexes are absent in mtDNA. Thus, DNA methylation may have an essential role in mtDNA [3].

Third, the regulation on crucial signaling molecules named ATP, acetyl-CoA, NADH, NAD, and S-adenosylmethionine, TCA enzymes, and their derivatives. Therefore, mtDNA can control the nuclear DNA gene expression through metabolism, signaling, growth, differentiation, and apoptosis [116]. A study used muscle biopsies from COPD patients, which showed an increase in cytochrome oxidase activity and an increase in ROS production. These results suggest mitochondrial dysfunctional associated with muscle dysfunction in COPD due to an increase in autophagy, apoptosis, and ROS production and reduction in oxidative capacity. These results are due to the peroxisome proliferator-activated receptor (PPARs) and PPAR- γ coactivator (PGC)-1 α is the critical regulator for mitochondrial biogenesis [117].

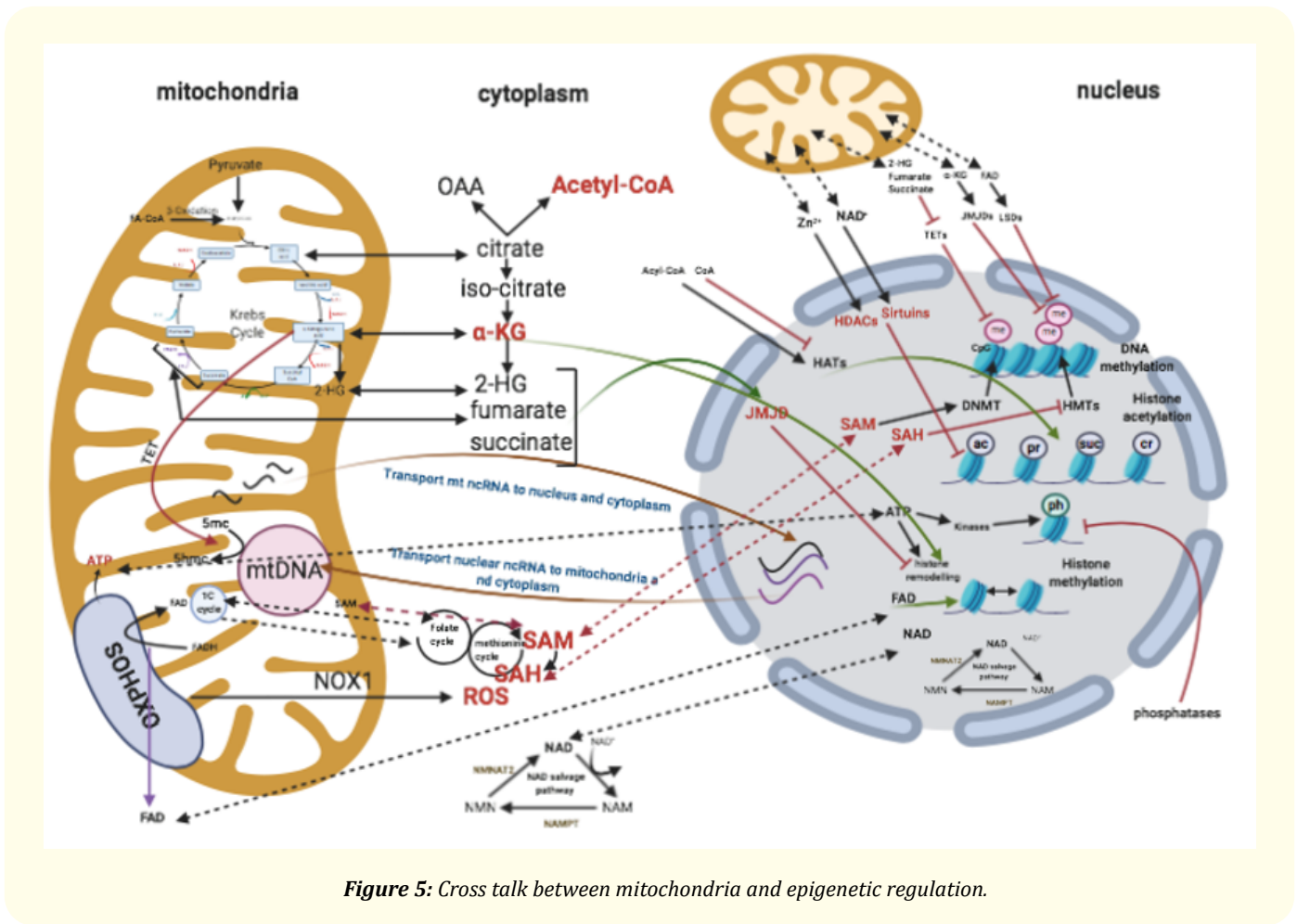


Figure 5: Cross talk between mitochondria and epigenetic regulation.

Next, chromatin modification required ATP through phosphorylation of histone tails explained in two parts. Part one, the unwind DNA process via a negative change of histone tail to initiate the transcription and replication, causing the mitochondrial energy to increase gradually for the process of gene expression in nuDNA. This high energy can maintain the DNA-protein binding at the phosphorylated state and impaired the sirtuins expression via increase the NAD⁺/NADH ratio, which allows unwinding the DNA for transcriptional initiation [115]. Histone deacetylase enzyme (HDAC 1/2) showed a reduction in macrophages and lung cells and related to COPD severity *in-vitro* [118]. The response to oxidative stress changed the intracellular of glutathione (GSH) that maintains the reduction condition of HDAC2 oxidative and post-translational modification states under the effect of coactivators on chromatin status driving or not the gene to activation or repression [118]. In the second part, the reduction level of ATP and acetyl-CoA affect negatively on the level of NAD⁺/NADH. Increasing the level of NAD⁺ enhanced the NAD⁺ III histone deacetylase (sirtuins) dependent. The depletion in ATP affects negatively on the phosphorylation amount resulting influence on DNA-protein binding interaction and signaling transduction pathway and increases the proton leak [21]. In airway epithelial cells, the exposure to CSE leads to a decrease in ATP level, inhibition in mitophagy, increase mitochondrial fragmentation, and reduction to IL-6, CXCL8 and IL-1β and cell senescence [119].

In addition, citrate is moving to cytosol from the TCA cycle, where it is transformed into acetyl-CoA and oxaloacetate for fatty acid synthesis (FAS) [115]. Viral infection can worsen the patient’s condition with COPD. FAS showed to be affected with rhinovirus in bron-

chial epithelial cells leading to a reduction of infection [120]. Moreover, the methionine cycle in mitochondria generates SAM, which is the primary cellular methyl donor of DNA and chromatin [115]. SAM synthesis provides a cysteine for glutathione synthesis. Glutamate, SAM, and cystathionine intermediates are all increased in TGF- β /FBS stimulated COPD [121].

Furthermore, 2-oxoglutarate (2-OG) is synthesized in the TCA cycle in mitochondria and then transferred to the cytosol to play an essential role in 5mC modification from DNA [115]. According to current research, there is not much research on the 2-OG. However, there is one research highlighted the importance of vitamin C in combination with 2-oxoglutarate, 5-hydroxy-methyl-furfur-aldehyde and carnosine interacting with free radicals and oxidants caused by tobacco smoke. This reaction could restore the anti-oxidative capacity of Vitamin C [122].

TCA products named Succinate and fumarate act as an inhibitor and interacting with JMJD domain-containing histone demethylase and TETs [115]. 5-hydroxymethylcytosine is the oxidized form of 5-methylcytosine catalyzed by Ten-eleven translocation (TET) enzymes. TET enzymes are an intermediate base, and 8-oxoglutarate is essential for oxidative stress. Both elements were found during DNA demethylation. Thus, smoking could lead to active oxidation of formyl and carboxyl, causing a reduction in the amount of 5hmc [78-91].

Citrate metabolism in cytosol generates 2-hydroxyglutarate (2-HG) from a mutated form of isocitrate dehydrogenation (IDH) [115]. Micro-RNA (miR-183) downregulate the (IDH2) results and Increase the CO₂ that inhibit the proliferation of alveolar cells and lung fibroblast, causing mitochondrial dysfunction [123]. Next, the influence of ROS on epigenetic signaling and its products from OXPHOS is controlled by transcription factors responsive to oxidative stress [115]. Nuclear CDC, like Kinase 1 (CLK1), maintains the mitochondrial homeostasis via regulating the genes in nuclear that have ROS depletion [124]. Moreover, the influence of molecular hydrogen (H₂) is a biologically active gas that used medically to trigger many pathological conditions. H₂ found to activate the transcriptional gene process is regulated by H3K27 methylation. H₂ promotes the H3K27 demethylase, jmjd3, changes the H3K27 methylation, and activates the mitochondrial unfolded protein response-related genes (mtUPR). This study suggests that molecular hydrogen can affect several pathological conditions positively. Because it activates mtUPR via epigenetic by gene expression change, this could highlight the impact of H₂ on COPD patients [125].

Finally, RNA modification is a dependent function and activities because RNA modifying enzymes encoded in the nuclear DNA and enzymes has to move to the mitochondria to provide the appropriate communication. The genome of mtDNA was highlighted in table 1. The tRNAs process occurs in cytoplasm as well as in mitochondria whereas the rRNAs is only occurs in mitochondria. Another ncRNA is miRNA which help to inhibit the gene expression via endogenous process called RNA interference leading to degradation of mRNA and its protein synthesis. MiRNA found in mitochondria as well as in nucleus raises many questions regarding their regulatory modification process and if the modification by nuclear encoded enzymes has recognition target and function and the way miRNA transmitted to mitochondria remains unknown. The communication was found in some studies. For example, a study was conducted a number of interleukin let-7 family members was enriched in mitochondria whereas interleukin let-7a and let-7b have interaction across several location in mitochondrial DNA. The modification in tRNA in post-transcription in nucleus since their enzyme is encoded in the nucleus; then translation occurs in cytoplasm and the protein synthesis is imported in mitochondria. Mt-rRNA modification are encoded only in the nuclear and the mutation of the enzymes were linked with human diseases. Other non-coding RNA named LncRNAs and mRNAs are not fully understood; however, there is some assumption showed mRNA and LncRNA modified within mitochondria [109-112,126].

Conclusion

Lung diseases are considered the leading cause of death worldwide. Lung infections, lung cancer and COPD are targeting millions of death recently. In the last few decades, there are efforts to understand the pathophysiology and the pathology of COPD due to its increase of morbidity and mortality rates. Airways epithelium cells play important role in maintain the airflow from and to alveoli and the first defense system for lung against pathogens and any inhaled from environments.

Airways epithelial cell types collaborate functionally with each other. However, there is a remain lack of knowledge about airway cells and the roles molecular mechanism responsible for COPD. The molecular interaction of airways cells, mucous and cilia cells, specifically epigenetic regulation remains unknown. Moreover, a subgroup cells located in secretory and goblet cells function, protein backbones, local environmental factors and metabolic regulation remained under investigation. In addition, oxidative stress by CS is critical issues for lung inflammatory response via the activation of stress kinase, redox sensitive transcription factors, mitochondrial dysfunction and epigenetic modification. Many targets that induce the pathogenesis of COPD in mouse need to be investigated in human as possible solution for biological treatment.

Genetic factors cannot explain the risk and prognosis of CS related diseases. Instead genetic factors can identify the genetic risk of COPD by identifying several gene mutations were involved in cellular pathways and protein miss-folded that may explain the early development and the heterogeneity of COPD by studying the molecular mechanism of each gene. Moreover, Lung aging in COPD in this review was highlighted from homeostasis decline process that affects lung functions in older age patients. Not only patients age, sex matched with and without COPD could link to type of chronic condition related with age between 55 - 65 years, the interconnected diseases such as obesity and anxiety, and the growth of pathologic aging associated with smoking [127].

Mitochondrial biology in relation to lung diseases still poorly understood. The dysfunction in mitochondria results increase in ROS, which coordinate between signaling pathways in relation with death and life in lung. The mitochondrial dynamic linked with abnormal mitophagy, which lead to apoptosis or necrosis. Another morphological changes undergoes in mitochondria is during the increase level of fission and fusion process in COPD whereas biogenesis process showed downregulation in COPD due to the loss of muscles and nutrients. MtDNA doesn't contain histones, but it contains acetyl-CoA via TCA cycle and S-adenosyl methionine (SAM) that used by histone enzymes. Moreover, mtDNA contains oxidative phosphorylation (OXPHOS). Therefore, the mitochondrial function and nuclear gene regulation are coordination bidirectional to modify the gene expression. Epigenetic involved in inflammation, cellular senescence and steroid resistance caused by CS exposure. In COPD, low expression of Histone HDAC2/SIRT1 is associated with DNA damage and repair, epigenetic instability, premature lung aging and chromatin modification. This cross talk between many epigenetic marks on histone and DNA methylation need a further understanding the post-translational modification that is regulated by ROS.

Small RNAs including non-coding RNAs don't have their roles fully understood; however, it showed that there is interaction with DNA by cis or trans-regulatory mechanisms, transcriptional, posttranscriptional, and posttranslational regulation of gene expression. MiRNA is probably the most studied; however, rest of small RNA still unknown [126]. Moreover; conducting the exosomal small RNAs mediate cell-to-cell communication which participate in lung diseases. Drug discovery in clinical trials reported results using miRNA. However, exosomal RNA technology could also become a potential biomarker for therapeutic and diagnostic target in lung [104].

Although there is an intensive research on epigenetic in metabolic organ function, it remains very little to know about epigenetic regulation in tissues specific. This could be very challenging due to the metabolic deregulation during diseases. In fact, the metabolic energy changes are the major contribution for many pathological diseases including COPD, which account half the death of worldwide. The future research could focus on the epigenetic-metabolic reaction in homeostasis and development condition as diseases prevention.

The communication between mitochondria and nucleus is regulated by depended factors and ncRNA, which present a novel focus on regulation network. However, some questions need to be highlighted regarding to what extend the pathological condition affect the mitochondria in epigenome and the role of mtDNA methylation. Another concern, whether the all mitochondrial stress response are regulated by the epigenetic and what signaling pathway do the mitochondria response in order to mediate the epigenetic changes in nucleus. However, to answer previous questions, we need to highlight some limitation in samples, techniques detection and the choice of the right tissues for the study. These factors are important for experimental design in epidemiological studies. The functional study focus should have a combination of analysis of mitochondrial epigenetic instead of separately represented. These studies are to understand the biologi-

cal relevance of change in epigenetic regulation of mitochondria. These studies could be investigated by the analysis of mitochondrial gene expression or functional assays [3,126,110-112].

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