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Review

Current views in chronic obstructive pulmonary disease pathogenesis and management

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) is a progressive lung dysfunction caused mainly by inhaling toxic particles and cigarette smoking (CS). The continuous exposure to ruinous molecules can lead to abnormal inflammatory responses, permanent damages to the respiratory system, and irreversible pathological changes. Other factors, such as genetics and aging, influence the development of COPD. In the last decade, accumulating evidence suggested that mitochondrial alteration, including mitochondrial DNA damage, increased mitochondrial reactive oxygen species (ROS), abnormal autophagy, and apoptosis, have been implicated in the pathogenesis of COPD. The alteration can also extend to epigenetics, namely DNA methylation, histone modification, and non-coding RNA. This review will discuss the recent progressions in COPD pathology, pathophysiology, and molecular pathways. More focus will be shed on mitochondrial and epigenetic variations related to COPD development and the role of nanomedicine as a potential tool for the prevention and treatment of this disease.

Contents

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1. Introduction

Chronic obstructive pulmonary disease (COPD) refers to a group of disorders that permanently impair the lung's function. These disorders include emphysema, a condition that involves damage to the wall's alveoli of the lung, and chronic bronchitis, which is long-term inflammation of the bronchi (WHO, 2021). According to the World Health Organization, COPD is the third leading cause of death worldwide, with 65 million people suffering from it and over 3 million people dying each year globally. It is also estimated that approximately 90% of the mortality rate occurs in low to middle-income countries (WHO, 2021). COPD prevalence and mortality are predicted to increase even more in the coming decades.

The clinical characteristics of COPD are shortness of breath on exertion, cough, and progressive disability. For the most part, treatment methods are palliative and designed to prevent further impairment due to infection (WHO, 2021). Several risk factors have been associated with COPD, including cigarette smoking (CS), occupational exposures, and aging. As COPD develops gradually, most exposures such as occupational exposure, biomass smoke, and CS take time to induce COPD. Of note, overlaps between the hallmarks of aging and COPD cellular processes have been reported, which implicates normal aging as a COPD facilitator (Antó et al., 2001; Kukrety et al., 2018; Mannino and Buist, 2007).

This review will explore the current advancements in COPD in terms of its pathology and pathophysiology, molecular pathways, its connection to aging, the associated mitochondrial and epigenetic changes in COPD, and it will shed more light on the mitochondrial epigenetics associated with COPD. Finally, the current role of nanomedicine in COPD as a tool for delivery, therapy, and diagnosis will be discussed.

2. Chronic obstructive pulmonary disease (COPD)

2.1. Pathophysiology of COPD

The vast majority of COPD is caused by the inhalation of cigarette smoke and other ruinous particles that could damage delicate lung tissues (WHO, 2019). The lungs' structure comprises increasingly fine tubules called the bronchial tree that ends with the alveolar sacs. The spongy lungs are also enriched in immune cells and have an innate defense system that repulses invaders and repairs injury. Most harmful immunological events occur on the bronchial cell wall barrier covered with hair-like organelles, cilia, and mucus

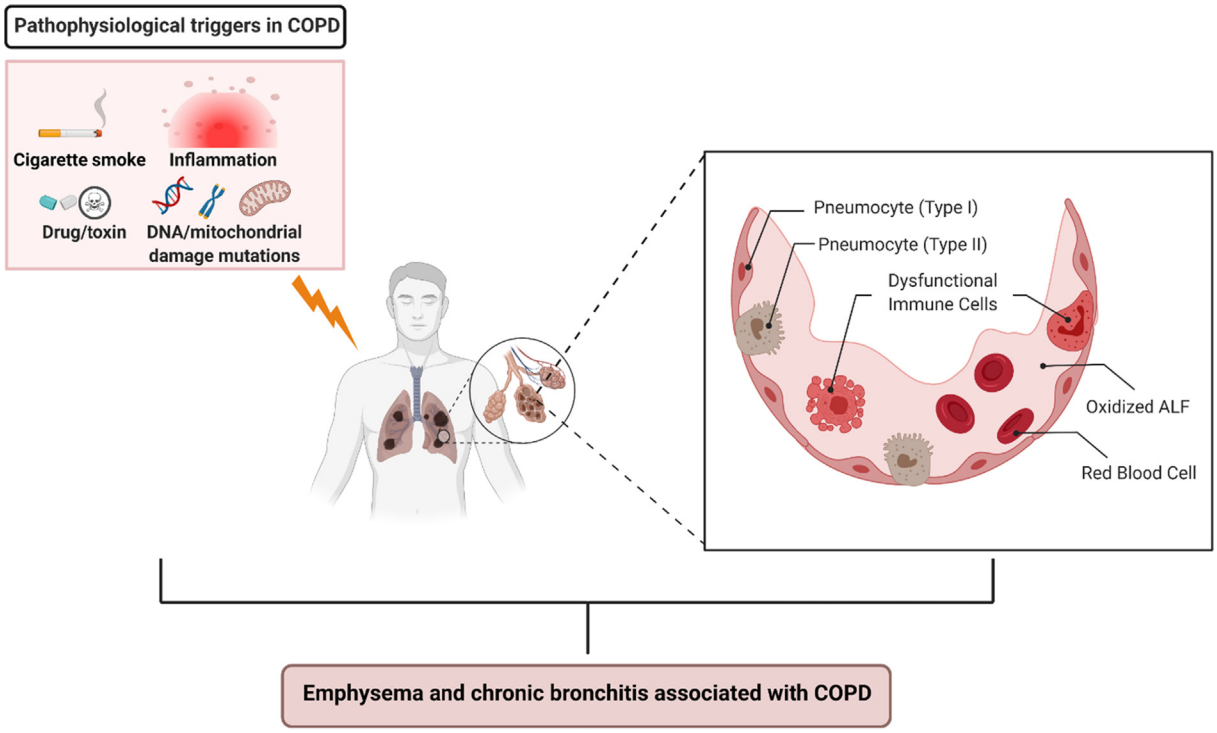

Fig. 1. Diagram illustrating the alveolus in lung tissue and the pathogenesis of COPD. Risk factors and drivers of COPD pathogenesis, showed in the **top left of the figure**, including cigarette smoking, which is the most common cause of COPD; inflammation, gene mutations, DNA damage, mitochondrial dysfunction, and exposure to drugs and toxins, resulting in an airway remodeling that induces emphysema and chronic bronchitis associated with COPD. The **right image** illustrates a cross-section of a distal airway and alveolar region, in which the surface of the lung contains different cell types, i.e., bronchial epithelium, epithelial basement membrane, and surfactant layers. Each alveolar tissue contains pneumocyte type I, pneumocyte type II, dysfunctional immune cells (macrophage cells), red blood cells, and capillary. ALF; alveolar lining fluid. Created with Biorender.com.

secreted by interstitial goblet cells. Mucus is constantly swept trapped inhalants out by the movement of cilia. The entry of foreign molecules could cause an abnormal inflammatory response that leads to smooth muscle contraction, mucus-gland hypertrophy, and mucosal edema. Consequently, chronic bronchitis and its symptoms such as increased airway wall thickness, mucus hypersecretion, ciliary dysfunction, and narrowed bronchioles occur (Wang et al., 2018).

Another condition of COPD is emphysema. When irritants and oxidative molecules reach alveolar epithelial cells (AECs), they initiate innate and adaptive immune responses. As a defense mechanism, AECs secrete cytokines, chemokines, and other factors to regulate the immune system. Alveolar macrophages also release destructive proteases such as elastases and matrix metalloproteinases (MMPs) in response to inflammation. The imbalance of proteases activity and apoptosis eventually leads to the destruction of the alveoli structure. In addition, collagen deposition accompanying the repair process worsens the condition as alveoli lose their elastic properties (Vij et al., 2018). Fig. 1 demonstrates the pathophysiological triggers in COPD.

2.2. Pathology of COPD

2.2.1. Inflammation and immune response

In COPD, the abnormal inflammatory response of peripheral airways and lung parenchyma involves innate immunity and adaptive immunity. The number of inflammatory cells such as macrophages, neutrophils, natural killer (NK) cells, and T-lymphocytes, linked through dendritic cells, increases parallelly with the progression of airflow limitation alveolar wall destruction, pulmonary neutrophil infiltration, and persistent infections (Trivedi et al., 2021). The inhalation of damaging particles actives epithelial and resident inflammatory cells such as macrophages, neutrophils, and eosinophils to release a variety of chemotactic factors, for example, CXC chemokines leukotriene B4 (LTB4), and Tumor Necrosis Factor (TNF-α), that play a crucial role in regulating the inflammatory response. As a result of CXCL8 and CXCL5 release, a marked increase in the number of macrophages and neutrophils has been observed in the bronchoalveolar lavage fluid (BALF) and sputum of the COPD patients. The circulating monocytes are also attracted in response to the chemokines CCL2 and CXCL1 secretion and directed towards sites of inflammation of the respiratory tract. In a recent study, healthy cigarette smokers were found to have high levels of CXCL8, CCL4, CCL17, and CCL22 compared to non-smoker suggesting a systemic upregulation of neutrophil and macrophage chemoattractant expression (Kim et al., 2015).

Furthermore, epithelial and bronchial smooth muscle cells, as well as alveolar macrophages, also recruit the adaptive immune cells, CD8+ cytotoxic T lymphocytes, and CD4+ T cells through the activation of CXC chemokine receptor-3 (CXCR3) mediated by the chemokines CXCL9, CXCL10, and CXCL11 (Henrot et al., 2019). The number of CD8+ cells is relatively higher than the number of CD4+ cells in COPD, releasing perforins and granzyme B and leading to cytolysis and apoptosis of the AECs (Barnes, 2017). Another chemoattractant, including LTB4, is produced during acute exacerbations to promote leukocyte migration, adherence, and the generation of reactive oxygen species (ROS). Alveolar destruction is caused mainly by ROS and serine proteases, elastolytic enzymes MMP-8, MMP-9, cathepsin G, and proteinase-3 secreted by neutrophils (Korkmaz et al., 2010).

2.2.2. Oxidative stress

The inhalation of cigarette smoke can induce oxidative stress, which is an important pathological feature of COPD (Repine et al., 1997; van Eeden and Sin, 2013). Cigarette smoke contains numerous oxidants and pro-oxidants capable of generating reactive ROS that damage lung cells. The overwhelming invasion of ROS depletes the protective antioxidants exogenously produced and causes harmful modifications of lipids, proteins, and DNA (Nita and Grzybowski, 2016). Nuclear factor E2-related factor (Nrf2) protects the lungs against oxidative stress by facilitating and up-regulating antioxidant proteins production. Nrf2 is typically bound to Kelch-like ECH-associated protein 1 (Keap1), which controls Nrf2′s homeostatic degradation by the ubiquitin–proteasome pathway in the cytoplasm (Ma, 2013). However, Nrf2 dissociates from Keap1 under oxidative stress conditions. It translocates into the nucleus to activate antioxidant response element (ARE) *via* the transcription of protective genes encoding antioxidant, anti-inflammatory, and enzymes that involve in anti-proliferation, detoxification, and xenobiotic metabolism (Raghunath et al., 2018).

In oxidative stress, the oxidative species level will rise than the level of their elimination systems, such as antioxidants which can induce cellular damage due to a disturbance of redox signaling and control (Luo et al., 2020; Sies et al., 2017). Damages caused by ROS are the leading cause of shorter lifespan and aging (Cadenas and Davies, 2000). The COPD incident is directly proportional to aging, in which the incident of acquiring COPD is rare in $\leq$ 40 years, whereas the epidemiology of COPD is significantly elevated above 10% at the age of greater than 40 years (Chapman et al., 2006). The oxidative damage that is occurred from aging can lead to several diseases, including COPD. This can be attributed to ROS, which causes damage to cells accumulated during aging (Yoon et al., 2019). The free radicals containing unpaired electrons, such as hydroxyl radical and superoxide, are highly reactive molecules and the leading cause of endogenous oxidative stress damage (Liochev, 2013). A high level of ROS can react irreversibly with several macromolecules, such as DNA, RNA, proteins, and lipids present in the nucleus and mitochondria, resulting in the formation and accumulation of harmful products that may cause cell damage if they exceed the repair capacity level of the cells (Luo et al., 2020).

ROS can damage the nucleic acids of DNA especially mitochondrial DNA, which is more susceptible to damage by ROS than nuclear DNA. The hydroxyl radical of the ROS can interact with any content of DNA such as pyrimidine, purine bases, deoxyribose sugar backbone leading to harmful changes such as single or double-stranded breaks in DNA (Phaniendra et al., 2015). For instance, telomeres are DNA sequences located at the ends of chromosomes responsible for protecting chromosomes from degradation or fusion with other chromosomes (Kukrety et al., 2018). ROS-induced damages to telomeres have less repair capacity than other parts of the chromosome in which the disrupted telomeres can accelerate aging and age-related diseases (Blackburn et al., 2015; von Zglinicki, 2000; von Zglinicki, 2002). The less repair capacity of telomeres could be attributed to the natural process of DNA replication in which telomeres will be shorter due to the inability of DNA polymerase to replicate chromosomes completely (Kukrety et al., 2018). Damage to DNA is the basis of genomic instability, cell cycle disruption, and cell death. High concentrations of ROS lead to DNA damage and telomere shortening, which are significant causes of cell senescence and the aging process (Selman et al., 2019).

RNA is more vulnerable to ROS damage for several reasons; since it is a single strand, unable to repair itself and the cytoplasmic RNAs are closer to the mitochondria (Phaniendra et al., 2015). Mitochondria is the primary source of ROS during respiration, and the electron transport chain from daily oxygen consumption may cause a leakage of 1–2% of all electrons that might occur even under normal conditions (Boveris and Chance, 1973; Liu et al., 2002). Hence, mitochondrial dysfunction is one of the major causes of a higher level of ROS production, which is directly related to aging (Hiona et al., 2010). SC can accelerate aging COPD because smoke contains harmful and reactive chemical species that gener-

ate free radicals (Cantin and Richter, 2012). Nevertheless, ROS must be at the physiological level at which the regulation of the reduction–oxidation-dependent signaling mechanisms is maintained. For instance, superoxide and hydrogen peroxide (H_2O_2) have a higher benefit in redox-dependent signaling due to their membrane permeability and stability, and therefore a low level of ROS can cause an adverse effect (Holmström and Finkel, 2014; Reczek and Chandel, 2015).

ROS can act as inflammatory stimuli. The cellular production of ROS, such as H_2O_2, is generally used as a redox signaling molecule to produce antioxidants enzymes and proteins containing cysteine residues (Schieber and Chandel, 2014). However, exposure to a high level of ROS interferes with the process of signal transduction (MacNee, 2005b; Reczek and Chandel, 2015). ROS could oxidize the reactive cysteine residue of a protein involved in redox signaling and oxidant resistance. Exogenous H_2O_2 mediates redox signaling through cysteine oxidation. The oxidation of active site cysteine thiols is reversible and plays an essential role in sensing the level of H_2O_2. However, a high level of ROS leads to excessive oxidization of the thiolate anion (S) that produces irretrievable oxidative species such as the sulfonic (SO3) and sulfinic (SO2) acid (Reczek and Chandel, 2015; Schieber and Chandel, 2014). H_2O_2 oxidizes protein tyrosine phosphatase (PTP) reactive cysteine thiols, impeding its activity to increase local protein tyrosine phosphorylation. Apoptosis and inflammasome assembly are also activated through cysteine oxidation (Reczek and Chandel, 2015; Schieber and Chandel, 2014). In addition, ROS downregulates the gene expression of E-cadherin through the activation of Rho-associated protein kinase (Forteza et al., 2012).

The entry of exogenous ROS through mucosal injury initiates innate immunity and triggers the release of cytokines and inflammatory mediators. Inhaled particles and endogenously released damage-associated molecular patterns (DAMPs) bind to pattern recognition receptors (PRR) present on the AECsand macrophages to generate signaling molecules, cytokines, and chemokines (Bianchi, 2007). As a response, stress-activated protein kinase (SAPK), such as mitogen-activated protein kinases (MAPKs), c-Jun NH2-terminal kinases (JNKs), and p38 MAPK families, are activated to regulate cell proliferation, autophagy, mitoptosis, apoptosis, and other biological processes (Arthur and Ley, 2013). JNKs may trigger intracellular signaling cascades. Nuclear factor-kappa-B (NF-κB) is translocated to the nucleus, and genes encoding cytokines and chemokines are transcribed, synthesized, and released to recruit more immune cells (MacNee, 2005a).

2.3. Genetic factor of COPD

Although CS is the most common cause of COPD, genetic factors can also increase the risk of developing COPD (McCloskey et al., 2001; Silverman, 2020). The genetic defect Z-allele in the *SERPINA1* gene, which is a hereditary disorder, leads to alpha-1-antitrypsin deficiency, and it is the most important genetic factor that contributes to the risk of developing emphysema. The *PI ZZ* deficient genetic type has 10–15% of alpha-1-antitrypsin average serum concentration. This low level of alpha-1-antitrypsin is highly insufficient for inhibiting neutrophil elastase and preventing lung parenchyma destruction (Zorzetto et al., 2008). Another genetic determinant of COPD is found in elastin gene mutations. Elastin is a significant constituent of cardiovascular and respiratory systems and plays a critical role in lung flexibility. Kelleher *et al.* have reported a mutation in human elastin resulting in the substitution of glycine 773 to aspartate (*G773D*), which weakens elastic fiber assembly (Kelleher et al., 2005). Over the past decade, a genome-wide association study (known as GWAS) and advanced approaches in comprehensive genomic analysis have been utilized to understand the genetic variants connected to COPD susceptibility and identify new genetic determinants. The number of these genetic associations has rapidly increased, and several recent studies have reported genes that link to structural and inflammatory alternations in the respiratory system (Hikichi et al., 2019; Ragland et al., 2019). However, more effort is needed to identify and assess new candidates genes in order to advance our understanding of COPD progression.

3. Mitochondrial alterations in COPD

Mitochondria are the primary energy source produced in the form of adenosine triphosphate (ATP) *via* oxidative phosphorylation (OXPHOS) in most eukaryotic cells, and they are vital organelles for nutrient and oxygen sensing. However, accumulating evidence suggested the crucial role of mitochondria in lung diseases pathogenesis through the regulation of critical cellular processes, including calcium homeostasis, mitochondrial ROS production, the release of pro-apoptotic factors, alteration of cellular metabolism, cell death, and inflammation. Human mitochondria consist of multi-copies of DNA, which vary from 100 to 10,000 copies per cell depending on the cell type and cellular energy need. Mitochondrial DNA (mtDNA) is organized as a circular double-stranded molecule built of 16,569 DNA base pairs, containing 37 genes essential for normal mitochondrial functions. One polypeptide component of the mitochondrial respiratory chain is encoded by 13 of the mitochondrial genome, while 24 genes are necessary for RNA translation mechanism, 2 genes for ribosomal RNAs (rRNAs), and 22 genes for transfer RNAs (tRNAs) (Dasgupta et al., 2020; Dromparis and Michelakis, 2013; Mishra and Chan, 2014; Nam et al., 2017; Schermuly et al., 2011).

Changes in mitochondrial respiration underlie the pathological mechanisms of many lung diseases, including COPD, asthma, and lung cancer. Chronic inflammation and dysregulated cellular responses of the lung upon CS exposure have been implicated in COPD pathogenesis, as shown in Fig. 2.

Many studies have shown that exposure to CS induces a reduction in mitochondrial OXPHOS (Mizumura et al., 2014; van der Toorn et al., 2007), while treatment with nontoxic concentrations of cigarette smoke extract (CSE) induces a metabolic shift from glycolysis to palmitate (β-oxidation) metabolism, resulting in increasing mitochondrial metabolic activity in lung epithelial cells (Ballweg et al., 2014; Hoffmann et al., 2013). Loss of succinate, a key component of the citric acid cycle and acetyl-CoA, was reported in basal cells of smokers (Deeb et al., 2016). In addition, dysregulated OXPHOS with increased cytochrome *c*-oxidase activity in airway smooth muscle cells, quadriceps, diaphragmatic, and external intercostal muscle of COPD patients was observed (Rabinovich et al., 2007; Ribera et al., 2003; Sauleda et al., 1998; Wiegman et al., 2015).

Changes in mitochondrial structure have been implicated in ROS generation in the pathological features of COPD (Jiang et al., 2017). Emerging evidence has revealed the direct relationship between the level of oxidative stress and mitochondrial fragmentation/elongation induced by CS (Hara et al., 2013; Hoffmann et al., 2013). Mitochondria are dynamic organelles that move across the cell along microtubules to where energy is most needed and constantly undergo fission or fusion to form mitochondrial networks (Youle and van der Bliek, 2012). The balance of mitochondrial proteins mediated fission and fusion processes plays a crucial role in forming new mitochondria and regulating mitochondrial respiration, morphology, and the cell cycle in response to mitochondrial or cellular stress (Mishra and Chan, 2014). Fusion of the outer mitochondrial membrane is controlled by the transmembrane GTPases, mitofusin-1 and mitofusin-2 (MFN1 and MFN2), whereas the fusion of the inner membrane is mediated by optic atrophy

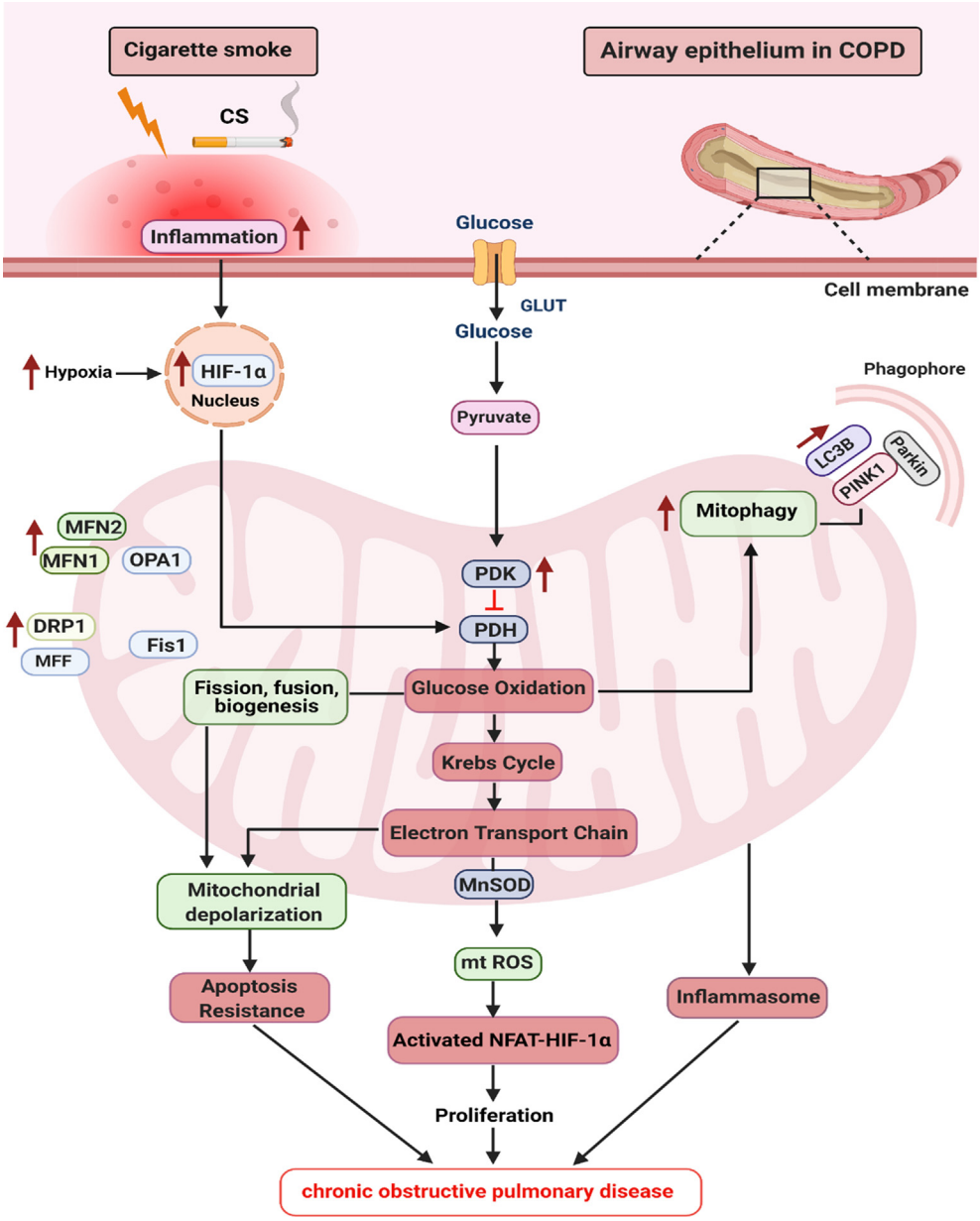

Fig. 2. Cigarette smoke-induced changes in mitochondrial function in COPD. Exposure to cigarette smoke and inflammation induce airway epithelium remodeling in chronic obstructive pulmonary disease. Impaired mitochondrial function, including fragmentation, mitochondrial ROS generation, mitochondrial membrane potential, mitophagy, lead to a metabolic switch from oxidative phosphorylation towards glycolysis. These changes are associated with increased expression of HIF-1α, mitochondrial fusion regulators, MNF2, MFN1, and OPA-1, fission modulators, DRP1, MFF, and FIS1, mitophagy markers LC3B, and Parkin, likely be linked to apoptosis-resistance, excessive proliferation, mitochondrial depolarization, and increased inflammation in airway epithelium in COPD. Red arrows indicate changes seen in COPD. Abbreviations: COPD, chronic obstructive pulmonary disease; CS, cigarette smoke; HIF-1α, hypoxia-inducible factor; MnSOD, manganese superoxide dismutase; mtROS, mitochondria-derived reactive oxygen species; NFκB, nuclear factor; PDH, pyruvate dehydrogenase; PDK, pyruvate dehydrogenase kinase; CLIC, chloride intracellular channel protein; LC3B, microtubule-associated protein 1-B light chain-3B; MFN1 &MFN2, mitofusin 1 &2; OPA1, optic. Created with BioRender.com.

protein-1 (OPA1). On the other hand, fission is regulated by a GTPase dynamin-related protein-1 (DRP1) and Fission-1 (FIS1) (Hoppins et al., 2007). Mitochondria in small airway epithelial cells of COPD patients' have shown numerous structural abnormalities, as they appear fragmented compared to smokers without COPD. Similarly, treatment with CSE induced mitochondrial fragmentation and membrane depolarization in the mitochondria from bronchial epithelial cells (Hara et al., 2013). The expression of MFN/OPA1 in lung epithelial cells was found to be up-regulated by CS, resulting in a hyperfusion of mitochondria, reduced stress resistance, and cellular senescence (Hoffmann et al., 2013). Mitochondrial fission is also induced by CS, in which DRP1 is translocated to mitochondria causing accumulation of fragmented mitochondria with increased ROS generation and enhanced cellular senescence (Hara et al., 2013). In response to cellular stress, an imbalance in homeostasis mechanisms including, mitochondrial biogenesis, mitochondrial dynamics (fission/fusion), and mitophagy may lead to mitochondrial dysfunction (Dromparis and Michelakis, 2013; Nam et al., 2017). Dysfunction or damaged mitochondria are selectively discarded through a process known as mitophagy, which is mainly regulated by post-translational modifications of phosphatase and tensin homolog (PTEN)-induced putative protein kinase 1 (PINK1) and Parkinson disease 2 (PARK2) (Kotiadis et al., 2014). Previous studies have demonstrated that

mitophagy protein PINK1, the necroptosis regulator RIP3 and the fission regulator DRP1 are highly increased in lung epithelial cells in human COPD (Araya et al., 2013; Kuwano et al., 2016). Evidence from several cohort studies showed that PINK1-PARK2-regulated mitophagy plays a vital role in the pathogenesis of aging-associated pulmonary disorders, such as COPD and idiopathic pulmonary fibrosis (Tsubouchi et al., 2018).

Evidence from several studies has shown a direct relationship between muscle dysfunction and mitochondrial dysfunction in skeletal muscle of COPD patients. Also, a significant increase in cytochrome oxidase activity and ROS production was observed in mitochondrial skeletal muscle of COPD patients, contributing to dysregulated mitochondria (Lloreta et al., 1996; Taivassalo and Hussain, 2016). Mitochondrial biogenesis and skeletal muscle oxidative capacity are controlled by peroxisome proliferator-activated receptors (PPARs) and PPAR-γ coactivator (PGC)-1α. (Remels et al., 2007). Previous studies have reported a reduction in the expression level of PPARs and PGC-1α, as well as transcription factor A mitochondrial (TFAM), which controls the mtDNA encoded gene expression and mtDNA copy number, in peripheral skeletal muscle of patients with moderate-to-severe COPD and muscle weakness (Remels et al., 2008; Remels et al., 2007; Taivassalo and Hussain, 2016). These findings regarding the signaling pathways of PGC-1α and the PPAR may provide novel targets that could facilitate the discovery of new potential therapeutic agents in COPD management (Remels et al., 2007; Taivassalo and Hussain, 2016).

4. Epigenetic alterations in COPD

Beyond the mutation at the DNA level, where it can cause a genetic disease such as COPD, other epigenetic modifications might be caused by different mechanisms, namely DNA methylation, histone modification, and non-coding RNA. All of which could play essential roles in DNA and chromatin modifications without affecting the nucleotide sequence (Berger et al., 2009; Bird, 2007; Ringh et al., 2019). DNA methylation is a process whereby a methyl group is transferred to cytosine and adenine residues. The methylation processes could be in different locations within the genome, for example, transcriptional starting sites, regulatory elements, and gene body, to regulate transcription (Ringh et al., 2019; Wu et al., 2016). The DNA methylation might also play an important role during the development stages, while external factors, such as diet and smoking, and internal factors, such as genetic variations, could influence the methylation processes (Dagar et al., 2018; Gallou-Kabani et al., 2010; Gao et al., 2016).

Different epigenetic mechanisms regulate the inflammatory pathways in the lung, including DNA methylation, where the alternation at pro-inflammatory cytokines could cause COPD (Brown et al., 2016; Tzortzaki et al., 2013). Several genome-wide methylation studies have found an association between DNA methylation and COPD developed through exposure to environmental factors such as CS and air pollution (Busch et al., 2016; Chen et al., 2021; Vucic et al., 2014). In an *in vivo* study, exposure to CS or air pollution has shown an alteration in the expression of the DNA methyltransferase (DNMT) genes (Sundar and Rahman, 2016). Other studies have evaluated the differences in the methylation status between smoker COPD patients and non-smoker COPD patients. In a cohort study led by Vries *et al.*, methylation profile was evaluated on 420,938 CpG sites on 1561 COPD patients (903 non-smokers and 658 smokers). Unexpectedly, there was no statistical difference between the two groups, while it was found in another study that non-smoking COPD patients developed DNA methylation alternation in different loci (de Vries et al., 2019; de Vries et al., 2018). Nevertheless, these studies were criticized for not conceding important factors, such as age and genetic variations, that could have influenced the epigenetic pattern.

The eukaryotic DNA is compacted together with histone proteins in a specific manner to form the chromatin. The histone is divided into two groups, linker histones (H1/H5) and core histones (H2, H3, and H4), which have a dynamic role on the activation or repression of gene expression, and can undergo post-translational modification by acetylation, methylation, phosphorylation, ubiquitylation, sumoylation, and citrullination (Lennartsson and Ekwall, 2009; McBryant et al., 2010). The process of histone acetylation, which is catalyzed either by histone acetyltransferases (HATs) or histone deacetylases (HDACs), regulates gene expression by the addition or removal of an acetyl group to lysine residues on the N-terminal tail from the histone core (Zong et al., 2015). This phenomenon could lead to the remodeling of the chromatin and control the accessibility of transcription activators. In general, the increased activity of acetylation is correlated with the induction of a pro-inflammation effect. CS has been found to induce acetylation, especially on the promoters of the pro-inflammatory genes at histones H3 and H4 (Clayton et al., 2006; Marwick et al., 2004). On the other hand, decreases in histone deacetylation, catalyzed by histone deacetylase 2 (HDAC2), in peripheral blood (Chen et al., 2012), and lung tissues (Ito et al., 2005), have been observed in COPD conditions.

Methylation occurs either on the lysine or the arginine amino acids of the histone H3 and H4, which could be modified by more than one methyl group. Unlike histone acetylation, histone methylation is more complicated, where the regulation of the gene expression is influenced by the locus of the amino acid and also by the number of methyl groups on histones (Bannister and Kouzarides, 2011; Barnes, 2009). In COPD, different patterns have been found; for instance, Qi Hui *et al.* have reported a substantial reduction of methylation in H4K20me2/3 of COPD patients, which is catalyzed by H4K20 di-methyltransferase SUV4-20H1 (Qi et al., 2021). In addition, the protein arginine methyltransferase 6 catalyzed the dimethylation at H3R2 was found to be downregulated in COPD patients (He et al., 2017). In addition, adding or cleaving ubiquitin-protein at the histone have a role in regulating the transcription activity (Nakagawa et al., 2008). A study done by Sundar and Rahman evaluated the expression of ubiquitin after exposure to CS *via* H292 cells to perform a quantitative polymerase chain reaction (qPCR) assay on a 24 h exposure to smoking. Almost 2.5-folds of an increase in the expression of Ube2b (Ubiquitin-conjugating enzyme E2 B - histone ubiquitination) and Usp16 (express Ubiquitin carboxyl-terminal hydrolase 16- histone deubiquitination) was observed (Sundar and Rahman, 2016). Nevertheless, other forms of histone modification by phosphorylation, sumoylation, and citrullination have not been extensively studied in COPD patients.

The vast majority of the human genome is not translated into proteins, while only around 2% is translatable (Clamp et al., 2007). From the non-translated part of the genome, various regulatory RNA molecules (non-coding RNAs, ncRNAs), including microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), are transcribed (Yoon et al., 2013). In a healthy state, ncRNAs play dynamic roles in regulating gene expression. The alterations in miRNAs function have been associated with the initiation and progression of diseases, such as cancer and Alzheimer (Mavrakis et al., 2010; Yan et al., 2015; Zhao et al., 2019) as well as COPD (Conickx et al., 2017a; De Smet et al., 2020; Xu et al., 2018). It was reported that CS downregulates miR-181c, which contributes to an inflammatory response, in smoking COPD patients, with a statistical P value of < 0.01 compared to non-smoker COPD patients (Du et al., 2017). The expression of other miRNAs, such as miR-218-5p (Conickx et al., 2017b), miR-146a (Osei et al., 2017), miR-101 (Hassan et al., 2012), and miR-34 (Velasco-Torres et al., 2019),

has also been correlated with COPD. Consequently, the expression of the miRNAs could be utilized as a biomarker for COPD diagnosis or identification for the disease state (Akbas et al., 2012; Leidinger et al., 2011; Salimian et al., 2018).

The lncRNAs interact and regulate different molecules such as DNA, miRNA, and protein leading to chromatin remodeling and transcriptional activation or suppression (Zhang et al., 2019). Bi Hui *et al*. conducted a comparative study of the alteration in the lncRNAs expression between COPD patients and non-COPD smokers using a microarray technique and found that 120 lncRNAs were up-regulated, especially RNA44121 was the most over-expressed, whereas 43 lncRNAs were downregulated and RNA43510, in particular, was the most under-expressed (Bi et al., 2015). In an *in vivo* study using an induced COPD mouse model, the expression of more than 100 lncRNAs was changed in comparison to the control mice (i.e., smoke-free housed mice) (Wang et al., 2017; Zhang et al., 2018). In the last decade, accumulating evidence has clearly supported the role of lncRNAs in COPD pathogenesis by altering different cellular and molecular pathways.

In addition to miRNAs and lncRNAs, circular RNAs (circRNAs) are recognized as a potential etiology for COPD. The circRNAs have demonstrated a significant control over some immune pathways, such as the NOD-like receptor signaling pathway and Th17 cell differentiation. A recent study done by Ruirui *et al*. found the dysregulation of 2132 circRNAs in 21 COPD patients compared to a control group of non-COPD (Duan et al., 2020). In another *in vivo* study, in which normal and COPD mice were treated for three months with fine particulate matter (<2.5 μm in diameter), it was found that 3,543 circRNAs were altered in the COPD model, while 6,718 circRNAs were up-regulated in the lung of normal mice. One of the up-regulated circRNAs (circBbs9) in both exposed models is associated with the cytokines upregulation and is known to induce NLRP3 inflammasome activation (Li et al., 2020).

5. Current and future perspective of nanomedicine in COPD

The traditional pharmacological strategies involved in managing COPD and its complications mostly ameliorates symptoms rather than curing the disease. Generally, they are different therapeutic agents such as bronchodilators, corticosteroids, and antibiotics, which could be administrated alone or in combination (Dixit et al., 2016). The lung is a highly complex organ composed of several physical and biological barriers that could hinder the proper delivery of COPD drugs to the site of action. The progression of COPD is usually associated with several biological cellular and non-cellular barriers, such as mucous hypersecretion, severe inflammation, and airway defense that may interfere with the proper delivery of therapeutics to the targeted tissue (Roy and Vij, 2010). Unfortunately, the complete curing of COPD using pharmacotherapy alone is not possible due to the biological barriers and poor bioavailability of used therapeutics (Burhan et al., 2013; Carvalho et al., 2011). A variety of inhaler devices are available to help the delivery and deposition of therapeutics directly to the lung of COPD patients. However, a large proportion of these drugs can deposit in the upper respiratory tract region; hence, poor bioavailability and effectiveness may occur (Thomas et al., 2008).

The potential emerging of nanoparticulate-based therapeutics in the treatment of COPD patients could revolutionize the current state of COPD management. Nanoparticle-based therapeutics could improve the efficacy of current COPD treatments, owing to their capability to deliver their loaded drugs deeply in the lung and crossing through the biological barriers (Vij, 2011). The efficiency of therapeutics cellular targeting and bioavailability could be enhanced by utilizing multifunctional nanoparticles with unique physicochemical and biological properties such as a large surface area to volume ratio, small particle size, biodegradability, and biocompatibility (Jiang et al., 2009). The use of nanoparticles may offer significant advantages for pulmonary administration of COPD therapeutics, including deep tissue penetration, protection of loaded drugs, enabling the sustained or controlled release, and enhanced cellular internalization and trafficking (Lai et al., 2009; Sung et al., 2007).

The development of the nanocarrier delivery system of COPD relies on overcoming the lung's physical and biological barriers by enhancing the pharmacokinetic profile of drug molecules inside the biological entity while targeting the diseased cells. One of the significant obstacles regarding the efficient management of COPD is the ability of administrated therapeutics to penetrate the thick and highly viscous mucus layer (Suk et al., 2011). Based on the physicochemical properties of nanoparticles, they play an essential role in mucociliary clearance, which is considered a potential parameter in developing and determining the effectiveness of pulmonary delivery systems (Blanco et al., 2015; Ratemi et al., 2016). Rytting *et al*. have reported the ability of small polystyrene nanoparticles with an average hydrodynamic diameter of about 100 nm to pass across the thick mucus layer much higher than the larger particle sized 250 nm (Rytting et al., 2008; Sanders et al., 2009). In terms of surface charge, the PEGylation of nanoparticles surface would neutralize the surface charge, facilitating the significant penetration of nanocarriers across the mucosal barrier and enhancing the overall therapeutic efficiency of the loaded drugs (Lai et al., 2009).

There are different types of nanotechnology-based materials that are currently used in the delivery of COPD therapeutics. Nanosized delivery systems are classified into two main groups: organic delivery systems (i.e., liposomes, polymers, and lipid-polymer hybrid nanoparticles) and inorganic delivery systems (i.e., gold, titanium dioxide, and cerium oxide nanoparticles) (Kuzmov and Minko, 2015). However, the application of nanoparticle-based therapeutics in COPD management is still in its early stages. Liposomes are among the most established nanoparticles platform that has been successfully utilized in the pharmaceutical fields, as several Food and Drug Administrations (FDA) has approved liposomal-based formulations. The liposomal nanosized delivery system is considered a good nanocarrier for combination therapy in COPD due to its ability to encapsulate hydrophilic, hydrophobic, and amphiphilic drug molecules (Pinheiro et al., 2011). The encapsulation of budesonide as a potent corticosteroid into liposomes nanoparticles has been reported to reduce cytotoxicity and improve the therapeutic efficiency in rat lungs (Janib et al., 2010). Nanoparticles have also been applied in combination therapy by loading two different drugs with different mechanisms of action in a single drug delivery system. Encapsulated formoterol (β2-selective receptor agonist) with beclomethasone (glucocorticoid steroid) in lipid-based nanocarriers have a significant therapeutic impact on the bioavailability of both drugs and reducing the undesirable side effects (van Rijt et al., 2014). Liposomes can be also formulated as dry powder inhalers in order to retain their size, drug payload, long-term stability, and avoid post-aerosolization aggregation. The nebulization of liposomal formulations as dry powder inhalers can be conducted *via* spray drying or freeze drying (Willis et al., 2012). In COPD patients, an effective therapeutic approach is targeting alveolar macrophages, which involve significantly in the pathogenesis of COPD, using fabricated anionic liposomes, as the negatively charged liposomes can be easily internalized by macrophages (Barnes, 2004).

Polymeric nanoparticles are also one of the emerging nanocarriers that could be used to deliver therapeutics in COPD patients. Vij *et al.* have designed a dual therapeutic strategy against COPD using a novel polymeric vesicle formed by poly (lactic-co-glycolic acid) (PLGA) and polyethylene glycol (PEG) mixture and loaded

with prednisolone and theophylline as a corticosteroid and anti-inflammatory bronchodilator, respectively. This formulation has successfully improved the therapeutic outcomes of COPD by improving the efficacy of both drugs (Vij, 2011). Several versatile biodegradable and biocompatible polymers, such as PEG, polyethyleneimine (PEI), polyethylene oxides (PEO), and polyvinyl alcohol (PVA), have been utilized in coat nanoparticles to enhance their drug delivery properties, reduce their cytotoxicity and immunogenicity, and facilitate their escape from the reticuloendothelial system (RES) (Suk et al., 2016). The loading of steroid drugs into polymeric micelles has been reported to reduce the inflammatory cell counts in the bronchoalveolar region in the COPD rat model (Sahib et al., 2011).

Lipid-polymer hybrid nanoparticles (LPNs) exhibit innate properties of both liposomes and polymers, offering an ideal cellular internalization in COPD therapy (Akinc et al., 2008). The encapsulation of a strong antioxidant dimeric manganese porphyrin (MnPD) into LPNs composing of 1,2-dioleoyl-3-trimethylammonium-propane (DOTAP) as a cationic lipid and PLGA as a biodegradable polymer demonstrated a marked elimination of ROS in an *in vitro* model of COPD. The effectiveness of LPNs may provide an alternative and a potential delivery system for COPD therapy (Chikuma et al., 2020).

Inorganic nanoparticles are widely used for the development of nanosized therapeutics and diagnostic tools in COPD. One of the extensively studied metallic nanoparticles is gold nanoparticles. These nanoparticles have been utilized in gene therapy delivering siRNA or DNA due to their cationic charge, which binds electrostatically to the negatively charged nucleic acid molecules. Gold nanoparticles have been developed as an inhaler to target the AECsin in a mouse model of COPD (Geiser et al., 2013). Titanium dioxide-based nanocarriers have also emerged as a potential approach in treating COPD since they cannot aggravate elastase-induced emphysema (Roulet et al., 2012). Cerium oxide nanoparticles could offer a promising candidate in COPD treatment due to their ability to protect lung cells from harmful ROS by mimicking the cellular enzymatic antioxidant activity of superoxide dismutase (SOD) and catalase (Passi et al., 2020). Superparamagnetic iron oxide nanoparticles coupled with anti-CD86 and anti-CD206 antibodies were developed as a non-invasive molecular imaging agent in the LPS-induced mouse model of COPD (Al Faraj et al., 2014). Oxidative stress is one of the critical pathological features in the disease progression of COPD. As mentioned earlier, mitochondrial oxidative stress and mitochondrial dysfunction might drive the oxidative stress-induced pathology (Wiegman et al., 2015). Selenium/silica (Se/SiO_2) nanoparticles possess an antioxidant property that has been reported to enhance the resistance against mitochondrial dysfunction *via* scavenging of ROS and maintaining the normal mitochondrial function (Wang et al., 2020). Despite the effectiveness of using metallic nanoparticles, there are concerning challenges, such as cytotoxicity, immunogenicity, low biocompatibility, degradability, and drug loading capacity, which limit their utilization (Su and Kang, 2020).

One of the recent therapeutic interventions in medical research is extracellular vesicles (EVs), particularly exosomes, which are currently under intense investigation. Cell membranes shed several components as vesicles, including apoptotic bodies, microvesicles, and exosomes (Almughem et al., 2021). EVs are small cellular membrane-bound vesicles found in body fluids (i.e., sputum, blood, and urine) and released by nearly all cell types. EVs may also play a crucial role in cell–cell communication by transferring information to recipient cells, influencing physiological and pathological conditions through the use of their bioactive cargo, such as DNA, RNA, miRNA, proteins, and other metabolites (O'Farrell and Yang, 2019).

To develop a good EV-mediated therapeutic delivery system, the cellular source of EVs should be prudently addressed. For instance, EVs derived from mesenchymal stromal cells (MSCs), which have regenerative capacity and anti-inflammatory properties, have been found to be a potential treatment for COPD (Broekman et al., 2018; Stolk et al., 2016; Weiss et al., 2013). Other factors, such as the culture condition, yield, manufacturability, and EV-mediated therapeutic route of administration, are additional concerns that should be considered (Wiklander et al., 2015).

EV-mediated gene delivery system, especially exosomes, could provide a potential therapeutic approach for COPD management. Adeno-associated vectors (AAVs) are a viral-based gene delivery system that has been widely used in gene therapy (Grimm and Büning, 2017). *In vitro* and *in vivo* applications of AAVs associated EVs (Exo-AAVs) have shown a significant improvement in the transduction efficiency and the neutralizing of anti-AAV antibodies compared to conventional AAVs (Maguire et al., 2012). This EV-mediated novel gene delivery system may hold the potential clinical application in COPD treatment by targeting the genetic disorder alpha-1 antitrypsin (AAT) deficiency (Quinn et al., 2020).

Immune cells targeting by nanoparticles could provide a potential treatment for inflammatory disease progression. Several immune and inflammatory cells contribute to the immune defense of the pulmonary system, such as dendritic cells, macrophages, mast cells, neutrophils, and basophils. A defect in the immune system negatively affects the lung, leading to the development of COPD. One of the immune cells significantly involved in inflammatory disease progression is macrophages, which play an integral function in innate immunity by secreting multiple pro-inflammatory cytokines and express respective surface markers after polarization (Hu et al., 2019). The M1 macrophages are a key factor of inflammation process by the release of pro-inflammatory cytokines, ROS, reactive nitrogen species, cyclooxygenase (COX)-2, and other kinds of cytokines, including TNF-α, IL-23, IL-1β, and IL-12, that lead to severe or chronic inflammatory condition (Gordon and Taylor, 2005). Therefore, targeting these types of immune cells using novel nano-based therapeutics is a potential approach to reduce the level of pro-inflammatory cytokines and control the disease progression.

Two methods have been used to target macrophages: macrophage depletion using nano-based therapeutics and macrophage re-education by nanoparticles carrying cytokines to the microenvironments. In the case of inflammatory diseases, the repolarization or downregulation of M1 macrophages to M2 macrophages is an effective strategy in inducing the release of anti-inflammatory factors and relieving inflammation (Ngambenjawong et al., 2017). The conjugation of nanoparticles *via* targeting ligands is an active approach that enables nanoparticles to target immune cells selectively. It has been reported that the conjugation of dextran ligand to nanoparticles surface has significantly improved the targeting of macrophages, hence increase the therapeutic efficiency (Ma et al., 2016). Moreover, targeting M1 macrophages using mannose conjugated polyethyleneimine nanoparticles leads to converting to M2 macrophages and increasing the release of anti-inflammatory mediators that help alleviate inflammatory disease progression (Alvarado-Vazquez et al., 2017).

Moreover, nanomedicine has been applied to target cell kinases to treat the underlying causes of the release of inflammatory mediators. For instance, several inhibitors of mitogen-activated protein (MAP) kinase pathways, such as the inhibition of extracellular signal-regulated protein kinases 1 and 2 (ERK1/2) pathway by PD98059, were used for the treatment of COPD (Mercer and D'Armiento, 2006; Mercer et al., 2004).Fig. 3 summarizes the different therapeutic approaches that are currently used to relive COPD symptoms and can be applied as potential therapies for COPD.

Several challenges and obstacles still lie ahead despite the potential advantages of using a nanosized delivery system in treat-

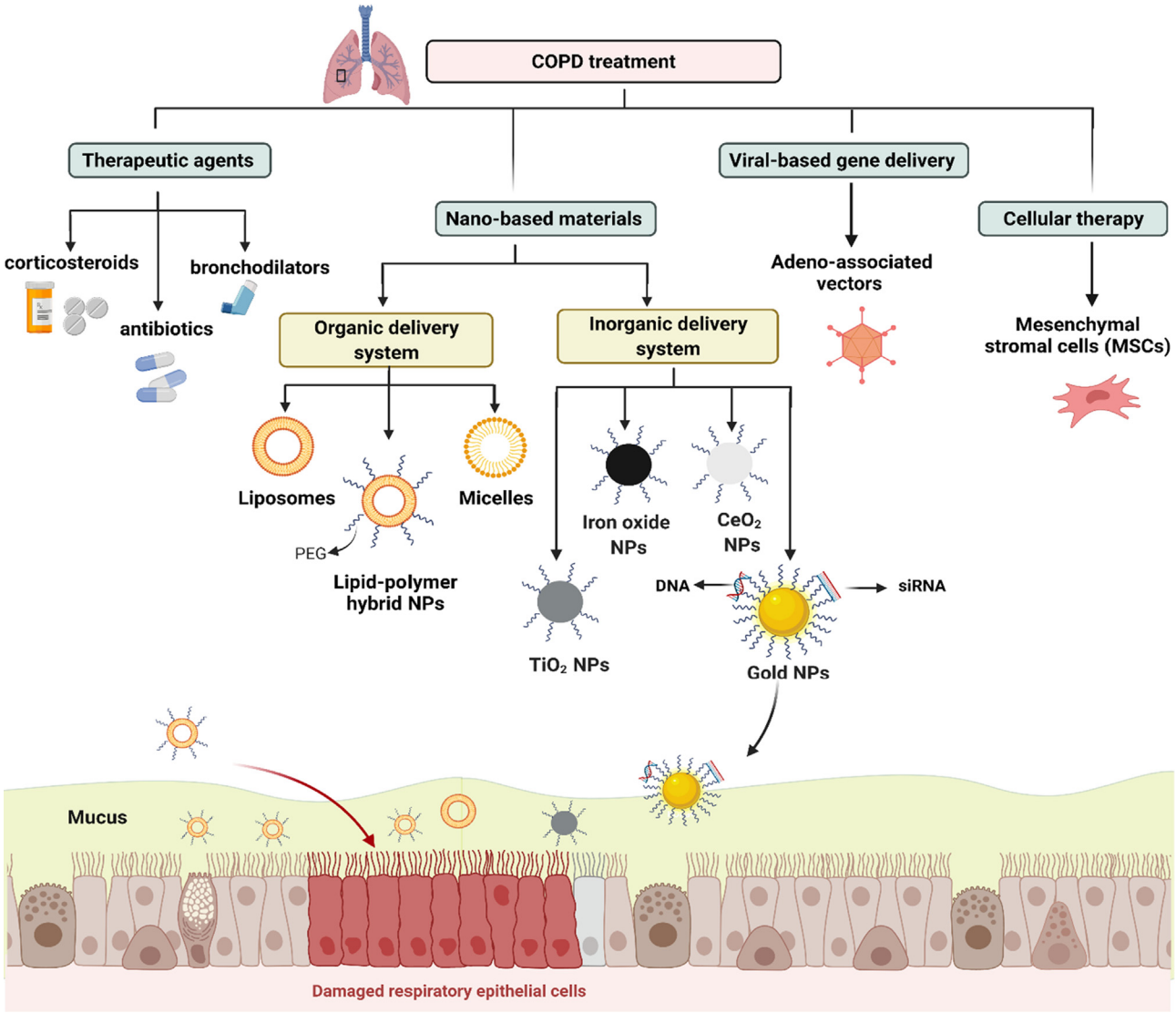

Fig. 3. Schematic diagram illustrating COPD treatment. There is currently no cure for COPD, and the existing therapies focus on helping patients cope with the symptoms. The conventional therapies include different classes of therapeutic agents such as bronchodilators, corticosteroids and antibiotics, which are administrated either alone or in combination. Nanoparticles-based delivery systems classify into two main groups; organic and inorganic delivery systems. Viral-based gene delivery system, such as adeno-associated vectors (AAVs), and cellular therapy, such as mesenchymal stromal cells (MSCs), hold potential clinical applications in COPD treatment. Abbreviation: NPs; nanoparticles, PEG; polyethylene glycol, TiO_2; Titanium dioxide, CeO_2; cerium oxide, siRNA; small interfering RNA. Created with BioRender.com.

ing COPD. To date, there is virtually no clinical trial that involves nanoparticle-based therapeutics for the treatment of oxidative stress in COPD. Regarding the application of nanoparticles as inhalers, the ideal aerodynamic diameter for the particles to deposit in the small airways and alveoli should be within the range of 1 to 5 μm, whereas the nanosized particles are susceptible to exhalation (Heyder et al., 1986; Sung et al., 2007).

6. Conclusion

COPD is considered one of the leading causes of death worldwide. In the last few decades, there have been tremendous efforts to understand COPD's pathophysiology and pathology. Although the molecular mechanism responsible for COPD has been investigated, many pathways involved in COPD development are influenced by a complicated network of interactions and factors. Hence, a therapeutic precision approach for individuals is important to prevent and treat COPD effectively. Oxidative stress and cell redox imbalance caused by CS are critical in the abnormal inflammatory response, whereas other significant COPD contributors, such as aging and genetics, may explain the individual pathology in COPD. Many studies have suggested the crucial role of mitochondria in COPD development. The dysfunction of mitochondria increases ROS production and the level of fission and fusion process in COPD. Since the mitochondrial function and nuclear gene regulation are bidirectionally coordinated in modifying gene expression, the biogenesis process in COPD showed downregulation due to the loss of muscles and nutrients. In addition, the mitochondrial dynamic is linked with abnormal mitophagy, which leads to apoptosis or necrosis. Exposure to environmental factors such as CS or air pollution also affects different epigenetic mechanisms, including DNA methylation, histone modification, and non-coding RNA epigenetic, leading to COPD. In addition, the communication between mitochondria and nucleus is regulated by dependent factors and ncRNA, which present a novel focus on the regulation network. However, more investigations are needed to know the pathological conditions that affect the mitochondria signaling to the epigenome, leading to epigenetic-mediated changes

in COPD. Additionally, metabolic energy changes are a significant contribution to many pathological diseases, including COPD. Future research could focus on disease prevention through studying the epigenetic and metabolic reactions in normal homeostasis and COPD conditions.

Although there are no effective pharmacological treatments for COPD, the potential emerging of nanotechnology has provided a viable platform for improving the treatment of lung diseases, and many clinical trials are being conducted worldwide to develop efficient therapy and nanotechnology-based strategies in overcoming the development of COPD. The future direction of nanomedicine in COPD could be achieved by approving a new nanosized delivery system that loads one or more therapeutic agents to enhance the therapeutic efficacy of these drugs or facilitate dual-action therapy.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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