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Review

Effects of $PM_{2.5}$ on Chronic Airway Diseases: A Review of Research Progress

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Abstract: The adverse effects of polluted air on human health have been increasingly appreciated worldwide. It is estimated that outdoor air pollution is associated with the death of 4.2 million people globally each year. Accumulating epidemiological studies indicate that exposure to ambient fine particulate matter ($PM_{2.5}$), one of the important air pollutants, significantly contributes to respiratory mortality and morbidity. $PM_{2.5}$ causes lung damage mainly by inducing inflammatory response and oxidative stress. In this paper, we reviewed the research results of our group on the effects of $PM_{2.5}$ on chronic obstructive pulmonary disease, asthma, and lung cancer. And recent research progress on epidemiological studies and potential mechanisms were also discussed. Reducing air pollution, although remaining a major challenge, is the best and most effective way to prevent the onset and progression of respiratory diseases.

Keywords: fine particulate matter ($PM_{2.5}$); chronic airway disease; health effects; inflammatory responses; oxidative stress; alveolar macrophages

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1. Introduction

In the past few decades, air pollution has become a major contributor impacting human health. More than 90% of the world's population live in locations where the air quality levels are far below the World Health Organization (WHO) standards. It is estimated that 4.2 million people worldwide die from lung cancer, heart disease, stroke, and acute and chronic airway diseases each year due to environmental air pollution [1]. Pollutants that have the greatest impact on human health include particulate matter (PM), sulfur dioxide, ozone, and nitrogen dioxide. The harmful impacts of PM on human health have become a major concern of the governments and health organizations around the world [2].

PM consists of solids and liquid droplets suspended in the atmosphere. PM is generally divided into three categories based on its aerodynamic diameter: coarse particles ($PM_{2.5–10}$) with a diameter of 2.5–10 μm, fine particles ($PM_{2.5}$) with a diameter equal or less than 2.5 μm, and ultrafine particles with a diameter less than 0.1 μm. PM differing in the source and chemical composition could lead to different health effects. $PM_{2.5}$ has a relatively small particle size, but a larger superficial area, which makes it easier to absorb all kinds of toxic substances. The Global Burden of Disease 2015 ranks $PM_{2.5}$ as the fifth highest risk factor for death [3]. $PM_{2.5}$ can enter the lung through breathing, deposit in the terminal bronchioles and alveoli, and even transport to other tissues and organs via the circulation system, causing multi-organ damage [4]. Results from our team and other epidemiological studies have found that $PM_{2.5}$ exposure is significantly associated with respiratory hospital admissions and mortality [5,6]. Several crucial studies have been summarized in Table 1.

In this paper, we summarized recent epidemiological studies by our team and others on the effects of $PM_{2.5}$ on the development of chronic airway diseases, including chronic obstructive pulmonary disease (COPD), asthma, and lung cancer, and discussed the potential mechanisms involved. A literature search was conducted using electronic databases

Pubmed, Web of Science, and Scopus, focusing on peer-reviewed English journal articles published in the last 5 years.

Table 1. Associations between $PM_{2.5}$ and chronic airway diseases.

Author, Year, Reference	Nationality	Population Sample	Health Effects	Main Findings
Pun et al., 2017 [5]	USA	529,000,000	COPD mortality	Per 10 μg/m^3 increase in $PM_{2.5}$ was positively associated with a 1.10-fold risk of COPD death (95% CI: 1.08, 1.12)
Doiron et al., 2019 [7]	UK	303,887	COPD prevalence and lung function	The odd ratio (OR) of COPD prevalence was 1.52 ([95% CI: 1.42, 1.62], per 5 μg/m^3). For each 5 μg/m^3 increase in $PM_{2.5}$ level was associated with lower FEV1 (−83.13 mL [95%CI: −92.50, −73.75]) and FVC (−62.62 mL [95%CI: −73.91, −51.32]).
Cortez-Lugo et al., 2015 [8]	Mexico	29	COPD symptoms	Per 10 μg/m^3 increment in $PM_{2.5}$ resulted in a 33% increase in cough symptoms (95% CI: 5-69%) and a 23% increase in sputum symptoms (95% CI: 2-54%)
Bao et al., 2020 [9]	China	54,058	AECOPD	The excess risk (ER) in the daily outpatient visits of COPD patients was 1.190% (95% CI: 0.176–2.215%, per 10 μg/m^3)
Chi et al., 2019 [10]	China	2251	asthma exacerbations	$PM_{2.5}$ was closely associated with asthma emergency department visits, with the strongest effects on lag5 (relative risks [RR] = 1.072, 95% CI: 1.024, 1.119)
Dunea et al., 2016 [11]	Romania	25	asthma symptoms	$PM_{2.5}$ was positively correlated with the number of wheezing episodes (r = 0.87; $p < 0.01$)
Hazlehurst et al., 2021 [12]	USA	1469	asthma prevalence	Each 2 μg/m^3 increase in $PM_{2.5}$ exposure was considered to be associated with a 1.29-fold increase in asthma risk (95% CI: 1.06, 1.58)
Abdul Wahab et al., 2019 [13]	Malaysia	514	Lung cancer histological types	Subjects exposed to $PM_{2.5}$ were twice as likely to develop lung adenocarcinoma as other types of lung cancer ($p = 0.024$)
Bai et al., 2019 [14]	Canada	100,146	lung cancer prevalence	The hazard ratio (HR) of per 5.3 μg/m^3 increment in $PM_{2.5}$ for lung cancer incidence was 1.02 (95% CI: 1.01–1.05)

2. $PM_{2.5}$ and Chronic Airway Diseases

2.1. COPD

COPD is a chronic inflammatory lung disease characterized by recurrent respiratory symptoms and persistent airflow restriction. It is the third leading cause of death worldwide [15]. Patients with COPD are more susceptible to the effects of ambient air pollution than healthy people. The ambient $PM_{2.5}$ is an important risk factor of COPD [16]. A recent study analyzed data from 303,887 individuals aged 40–69 years from the UK Biobank and found that higher $PM_{2.5}$ concentration was significantly associated with COPD prevalence. It was also demonstrated that for every 5 μg/m^3 increase in the concentration of $PM_{2.5}$, the forced expiratory volume in 1 s (FEV1) and the forced vital capacity (FVC) decreased by 0.083 and 0.063 L, respectively [7]. Another study found that a short-term $PM_{2.5}$ exposure in COPD patients was associated with decreased FEV1, FVC, carbon monoxide diffusing capacity, and maximal mid-expiratory flow, indicating that $PM_{2.5}$ may affect airway function and pulmonary dispersion function in patients with COPD [17].

$PM_{2.5}$ exposure is associated with acute exacerbation of COPD (AECOPD). In an adult cohort study in Mexico, per 10 μg/m^3 increment in $PM_{2.5}$ resulted in a 33% increase in cough symptoms and a 23% increase in sputum symptoms [11]. We found that in Lanzhou, China, per 10 μg/m^3 increase in $PM_{2.5}$ level led to a 1.190% increase in the daily outpatient visits of COPD patients. Moreover, for every 10 μg/m^3, the daily outpatient visits increased by 0.978% for those aged <65 years old and 1.906% for those aged ≥65 years old, suggesting that $PM_{2.5}$ exposure had a greater impact on the elderly [9]. Consistently, epidemiological studies performed in other countries or regions revealed a clear correlation

between increased $PM_{2.5}$ exposure and COPD-related hospital visits [18–21]. A meta-analysis combining the results of 12 cohort studies showed that an increase of 10 $\mu g/m^3$ in ambient $PM_{2.5}$ is associated with a 3.1% increase in the hospitalizations for COPD [22]. Seasonal changes have an impact on the association between $PM_{2.5}$ exposure and AECOPD. Our study showed that $PM_{2.5}$-related COPD outpatient visits were higher in winter than in summer [9]. Other cohort studies also suggest a stronger correlation between $PM_{2.5}$ exposure and COPD hospitalizations in cold weather [19,21,23]. However, Samoli et al. [24] indicated that the association of $PM_{2.5}$ exposure and COPD outpatient visits was stronger in warmer seasons. Another study in Yinzhou, China also noted that the effects of $PM_{2.5}$ on hospitalizations for COPD was stronger in the warm season (April to September) than in the cold season (October to March) [18]. The discrepancy of seasonal impact of $PM_{2.5}$ on COPD patients might be related to differences in $PM_{2.5}$ component and levels and human activities. However, this needs to be further investigated.

The effects of $PM_{2.5}$ on the risk of COPD death has been rarely studied, and the conclusions are inconsistent. A cohort study of older adults in the United States investigated the correlation between ambient $PM_{2.5}$ exposure and the rate of mortality [5]. After adjusting for possible influencing factors, a 12-month mean $PM_{2.5}$ exposure concentration (per 10 $\mu g/m^3$ increase) was positively associated with a 1.10-fold risk of COPD death. Date from the European MED-PARTICLES project during 2001–2010 suggested that every 10 $\mu g/m^3$ increase in atmospheric $PM_{2.5}$ over 6 days was relevant to a 2.53% increase in COPD death [24]. In addition, long-term exposure to $PM_{2.5}$ may be responsible for the increased risk of cardiovascular death in patients with COPD [25]. However, other studies had different conclusions. A population-based cohort study conducted in Canada failed to demonstrate a significantly positive correlation between $PM_{2.5}$ and the risk of COPD death after adjusting for confounding factors [26]. Another study by Uccelli et al. [27] found no association between $PM_{2.5}$ and the rate of COPD death in central Italy.

At present, the pathogenesis of $PM_{2.5}$ in COPD primarily focuses on inflammatory response, oxidative stress, immune disorder, and cytotoxicity. $PM_{2.5}$ exposure induces airway inflammation in mice by increasing the infiltration of inflammatory cells, including macrophages, neutrophils, and eosinophils (EOS). These cells secrete pro-inflammatory molecules, such as interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF)-α [28–31]. Repeated $PM_{2.5}$ also resulted in decreased pulmonary function and emphysema, even at a lower level [31]. $PM_{2.5}$ dose-dependently upregulates the expression of matrix metalloproteinase (MMP-9), MMP-12, fibronectin, collagen, and transforming growth factor (TGF)-β1, in which the increased protease activity is highly related to airway remodeling and development of emphysema in COPD [32]. Of note, $PM_{2.5}$ exposure could significantly worsen cigarette smoking (CS)-induced changes in COPD, suggesting that $PM_{2.5}$ and CS may synergistically promote the occurrence and the development of COPD. Our previous studies showed that $PM_{2.5}$ can obviously reduce the levels of total antioxidant capacity (TAC) and glutathione peroxidase (GSH-Px), and increase the level of malondialdehyde (MDA) in the lungs of COPD mice, suggesting that the oxidation/antioxidant imbalance was aggravated in COPD after $PM_{2.5}$ exposure [33,34]. The change in this balance will increase oxidative stress and promote airway inflammation. We found that nuclear factor-related factor 2 is a key mediator of $PM_{2.5}$-induced oxidative stress exacerbation [33]. In addition, $PM_{2.5}$ is involved in the immune dysfunction of COPD. Our group have shown that exposing COPD mice to $PM_{2.5}$ triggered the imbalance of helper T cells (Th)1/Th2 and Th17/regulatory T cells (Treg) in the T lymphocyte subsets by activation of the Notch pathway [35].

Alveolar macrophages (AMs) play a role in preventing $PM_{2.5}$-induced AECOPD (Figure 1). He et al. [36] have shown that $PM_{2.5}$-bound lipopolysaccharide (LPS) promoted the expression of IL-6, cyclooxygenase-2, and heme oxygenase-1 (HO-1) in AMs in COPD mice via a myeloid differentiation factor 88 (MyD88)-dependent pathway. We have found that LPS significantly upregulated the expression of Toll-like receptor 2 (TLR2) and TLR4 and increased the levels of pro-inflammatory cytokines in monocyte derived macrophages

(MDMs) isolated from patients with COPD [37]. Furthermore, MDMs derived from patients with COPD showed decreases in the expression of TAC and GSH-Px and an increase in the expression of MDA, indicating that COPD patients are under oxidative stress, and that the oxidative stress is aggravated by exposure to $PM_{2.5}$ or CS [33]. Excessive oxidative stress may be responsible for the decreased phagocytic capacity of MDMs following $PM_{2.5}$ exposure [38]. In support of this notion, our in vivo studies demonstrated that either acute or chronic exposure to $PM_{2.5}$ impaired AMs phagocytosis in COPD mice through intensifying oxidative stress [34,39,40]. Our further study showed that actin-related protein 2/3 complex and F-actin mediated abnormal cytoskeletal rearrangement in response to $PM_{2.5}$, which aggravated the decline of AMs phagocytosis in COPD mice [41]. It has been shown that $PM_{2.5}$-dependent activation of phosphatidylinositol 3-kinase δ (PI3Kδ) and inhibition of RAS homologous gene family member A activity were associated with abnormal cytoskeletal rearrangement in AMs [42]. Our studies also suggest that traditional Chinese medicine, such as Astragalus and Codonopsis pilosula polysaccharides, had protective effects on the phagocytosis of AMs in COPD mice exposed to $PM_{2.5}$ [34,39]. Moreover, the direction of AMs polarization induced by $PM_{2.5}$ still remains controversial. It has been shown that $PM_{2.5}$ can promote the polarization of AMs towards a M1 phenotype by a reactive oxygen species (ROS)-dependent mechanism, which is associated with oxidative stress [30]. In contrast, $PM_{2.5}$ has also been shown to enhance an M2 phenotype and promote the expression of MMP-9, MMP-12, and TGF-β in lung tissues [43].

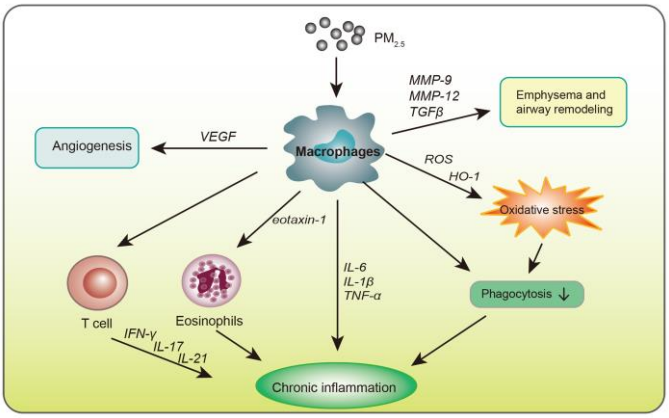

Figure 1. The role of macrophages in $PM_{2.5}$-related chronic airway diseases. $PM_{2.5}$ exposure promotes recruitment of macrophages and release of cytokines, such as IL-6, IL-1β, and TNF-α. Macrophages also release eotaxin-1 to attract eosinophil recruitment, and stimulate T cells to produce IFN-γ, IL-17, and IL-21. $PM_{2.5}$ induces macrophage phagocytosis dysfunction, which is related to oxidative stress. Above effects leads to chronic lung inflammation. The increased expressions of ROS and HO-1 in macrophages aggravates pulmonary oxidative stress. MMPs and TGF-β released by macrophages are involved in the process of emphysema and airway remodeling. In addition, macrophages involved in tumor angiogenesis by releasing VEGF.

It has been demonstrated that $PM_{2.5}$ probably elicits autophagy of human bronchial epithelial cells (HBECs) by enhancing ROS-mediated oxidative stress [44,45]. Autophagy functions to maintain cell homeostasis and adapt to stress under normal conditions, whereas excessive autophagy results in cell death. Similarly, it has been reported that HBECs produced nitric oxide synthase 2 and nitric oxide in vitro when exposing to $PM_{2.5}$, which resulted in autophagy-mediated cell death [46]. Excessive production of ROS contributes to mitochondrial damage and HBEC apoptosis, linking to the development of emphysema [31,47]. Li et al. [48] indicated that $PM_{2.5}$ exposure down-regulated the expression of microRNA (miR)-486, which caused ROS production and apoptosis of HBECs. $PM_{2.5}$ also up-regulated long-noncoding RNA MEG3 and triggered p53-mediated apoptosis and autophagy in HBECs [49]. Together, these findings suggest that $PM_{2.5}$ induces HBECs autophagy and apoptosis by epigenetic mechanisms.

2.2. Asthma

Asthma is a complex heterogeneous disease characterized by chronic inflammation, reversible airflow limitations, and airway hyperresponsiveness [50]. Asthma affects approximately 300 million people worldwide [51]. There is growing epidemiological evidence that $PM_{2.5}$ exposure can lead to deterioration of lung function and acute attacks in asthmatic children and adults. In a Canadian panel study of school-age children with asthma, exposure to trace metals in $PM_{2.5}$ was associated with elevated exhaled nitric oxide [52]. A two-year study of asthma patients conducted by Duan et al. [17] showed that every 10 $\mu g/m^3$ increase of $PM_{2.5}$ at lag 3 reduced FEV1 by 0.012 L, FVC by 0.042 L, and the peak expiratory flow (PEF) by 0.061 L/s, suggesting that a short-term $PM_{2.5}$ exposure was negatively correlated with FEV1, FVC, and PEF. A recent meta-analysis review study showed that ambient $PM_{2.5}$ was negatively associated with FEV1/FVC in adults with asthma in general, despite the low or moderate risk of bias in some selected studies [53].

Currently, $PM_{2.5}$ is generally believed to be relevant to asthma exacerbations in which children are more susceptible than adults [10,54]. It is estimated that $PM_{2.5}$ contributed to 5–10 million of emergency department visits by asthma patients in 2015, accounting for 4–9% of total visits worldwide [55]. To date, studies have confirmed that $PM_{2.5}$ is the only compound that is independently related to emergency department visits for asthma patients [56,57]. Moreover, a case-crossing study from South Texas has shown that elevated $PM_{2.5}$ concentration increased the risk of readmissions in children with asthma [58]. Wheezing is a primary respiratory symptom to assess exogenous factors that trigger asthma attacks. In a study of allergic children in Romania, $PM_{2.5}$ was positively correlated with the number of wheezing episodes [11].

Schultz et al. [59] reported that the risk of asthma was increased by more than three times for each 5 $\mu g/m^3$ increase in annual average concentration of $PM_{2.5}$. Interestingly, even a level of $PM_{2.5}$ well below WHO guidelines was also linked to an increased morbidity of asthma and an increased risk of childhood sensitization to common allergens [60]. Moreover, a study of 4140 children in Southern California over 11 years demonstrated that reductions in environmental $PM_{2.5}$ were significantly correlated with the lower asthma rates [61].

Exposure to $PM_{2.5}$ early in life may increase an individual's risk of developing asthma. A population-based birth cohort study observed that a 2.7-fold increase in $PM_{2.5}$ in the first year of life was related to an absolute 4.1% increase in asthma risk by age 5 [62]. The impacts of $PM_{2.5}$ on asthma and wheezing in children can be traced back to embryonic development in the womb. Yan et al. [63] reported that prenatal exposure to $PM_{2.5}$ increased the risk of asthma and wheezing in children, and was more strongly associated with the risk of asthma in children under 3 years of age. Recently, a large multi-city sample study in the United States suggests that fetal lung development during 26–36 weeks of gestation is susceptible to the toxicity of $PM_{2.5}$. Their study showed that each 2 $\mu g/m^3$ increase in environmental $PM_{2.5}$ exposure was considered to be associated with a 1.29-fold increase in asthma risk [12]. A large birth cohort in Taiwan, China has also shown the adverse effects of prenatal and postnatal exposure to $PM_{2.5}$ on the development of asthma in children [64].

Asthma is associated with Th2 airway inflammation with prominent infiltration of EOS and the production of pro-Th2 cytokines, including IL-4, IL-5, and IL-13 [50,65]. $PM_{2.5}$ exposure can exaggerate the effects of allergens in asthmatic mice, leading to increased airway hyper-responsiveness and Th2 cytokine levels, and aggravation of Th1/Th2 cell immune imbalance [66,67]. IL-33 and IL-25 are newly discovered Th2 cytokines. $PM_{2.5}$ promotes the release of IL-33 and IL-25 to drive the Th2-biased immune response [68,69]. Nuclear transcription factor-κB (NF-κB), GATA binding protein 3, T-box transcription factor, and Runt-related transcription factor 3 are involved in Th1/Th2 immune imbalance induced by $PM_{2.5}$ [66,70]. Our previous study indicated that the Notch pathway plays a vital role in immune imbalance in asthma [71]. In another unpublished study, we found that Notch pathway may link to $PM_{2.5}$-induced Th1/Th2 immune response in asthmatic mice. Th17/Treg imbalance is associated with asthma severity. Trace-elements that bind to $PM_{2.5}$,

such as polycyclic aromatic hydrocarbons, may be a strong candidate to regulate Th17/Treg imbalance. $PM_{2.5}$ targets glutamic oxalacetic transaminase 1 and hypoxia inductive factor (HIF-1α) in an aromatic hydrocarbon receptor-dependent manner, shifting Th17/Treg towards a Th17 predominance [72].

Increased EOS recruitment after $PM_{2.5}$ exposure is associated with the severity of airway inflammation in asthma [73]. During sustained $PM_{2.5}$ treatment, the JAK/STAT6 and TLR2/TLR4/MyD88 pathways have been shown to regulate EOS recruitment [73,74]. Long-term exposure to $PM_{2.5}$ aggravates asthma by promoting the polarization of M2 macrophages. The release of serum eosinophil chemokine (eotaxin-1) by M2 macrophages may be another important reason for the increase of eosinophilic infiltration in asthma [75].

$PM_{2.5}$ can up-regulate IL-17 and TNF-α and down-regulate integrin β4 levels, which together aggravate neutrophil airway inflammation in asthma model [76,77]. $PM_{2.5}$ also affects neutrophil-related responses, such as neutrophilic extracellular traps (NETs), in a ROS-dependent manner. NETs up-regulate the levels of quinone oxidoreductase, promote the expression of MUC5AC and mucus over-secretion, leading to aggravation of the asthmatic symptoms [78].

Functional and structural defects in HBECs exacerbate the severity of asthma. Exposure to $PM_{2.5}$ induces an increase in ROS levels and inhibits the expression of Stanniocalcin 2, the components of tight junctions, ultimately resulting in epithelial barrier damage [79,80]. Disruption of this barrier function is accompanied by the secretion of pro-inflammatory mediators and activation of the oxidative stress pathways, including mitogen-activated protein kinase and NF-κB [80].

2.3. Lung Cancer

The International Agency for Research on Cancer classifies outdoor air pollution and $PM_{2.5}$ as class I carcinogens for lung cancer [81]. Numerous studies have identified that exposure to air pollution, particularly $PM_{2.5}$, is positively correlated with the morbidity and the mortality of lung cancers [5,82,83]. Repeated outdoor $PM_{2.5}$ exposure is related to the risk of lung cancer death among never-smokers [84]. A prospective study involving 89,234 Canadian women found that environmental $PM_{2.5}$ even at a low concentration was correlated significantly with the incidence of lung cancer. The study also showed that the relationship between $PM_{2.5}$ exposure and lung cancer occurrence varied greatly by histological types, with an increased risk of small cell carcinoma by 53% and adenocarcinoma by 44% [85]. Similarly, two studies from Europe and Malaysia indicated a significant association between ambient $PM_{2.5}$ exposure and lung cancer, particularly adenocarcinoma [13,86]. In addition, Guo et.al [82] conducted a nationwide analysis in 295 Chinese cities from 2006 to 2014 and found that $PM_{2.5}$ has a long-term lag effect on the incidence of lung cancer.

Yang et al. [84] compared the characteristics of lung cancer between China and the United States. The study showed that the morbidity of non-smoker patients with lung cancer in China was significantly higher than that of the United States. In China, the mortality of lung cancer caused by $PM_{2.5}$ was 18% for women and 10% for men, suggesting that women have a higher risk of developing lung cancer attributable to $PM_{2.5}$ than men. Diagnosis of lung adenocarcinoma was dominated by women and non-smokers, and subjects exposed to $PM_{2.5}$ were twice as likely to develop lung adenocarcinoma as other types of lung cancer [13]. In contrast, some studies have revealed that lung cancer incidence correlated with $PM_{2.5}$ was more significant for males [83,87]. The effect of age on $PM_{2.5}$ associated lung cancer remains controversial. One cohort study on continued exposure to outdoor air pollution and lung cancer morbidity showed that $PM_{2.5}$ exposure had a greater effect among younger individuals [14]. Another study suggested that $PM_{2.5}$ was associated with increased mortality of lung cancer among older adults [87].

$PM_{2.5}$ can directly promote the proliferation, migration, and invasion of lung cancer cells [88–90]. Lin et al. [91] found that combined exposure to $PM_{2.5}$ and cigarette smoke extract stimulated autophagy of lung cancer cells, leading to increased cell migration, invasion, and epithelial mesenchymal transformation (EMT). Epithelial cells undergoing EMT

show higher motility and aggressiveness, increasing resistance to apoptosis and chemotherapy drugs, and even development of stem cell-like characteristics [92]. Cancer stem cells (CSC) are also potential drivers of tumor initiation and progression. Chronic exposure to $PM_{2.5}$ can lead to the occurrence of EMT and CSC in vivo and vitro [88,92,93]. Oncogenic pathways, including Notch, Smad, HIF-1α, and PI3K/Akt pathways, have been shown to be involved in $PM_{2.5}$-induced EMT process and facilitate tumor progression [90,92,94,95].

$PM_{2.5}$ exposure leads to genetic and epigenetic abnormalities that play prominent roles in lung carcinogenesis. RNA sequencing analysis has shown that on $PM_{2.5}$ treatment resulted in altered expression of 143 genes, including 66 up-regulated genes and 77 down-regulated genes, in human non-small cell lung cancer (NSCLC) cell lines [96]. $PM_{2.5}$ can affect DNA methylation and the cell cycle. Inactivation of p53 by genetic or epigenetic mechanisms is an oncogenic driver of lung cancer. An in vitro study demonstrated that repeated exposure to low doses of $PM_{2.5}$ induced hyper-methylation of p53 promoter by increasing expression of DNA (cytosine-5-)-methyltransferase 3β (DNMT3B), leading to p53 silencing. The study also found that up-regulation of DNMT3B expression was attributed to activation of the ROS/protein kinase B pathway [97]. In another study, lung cancer cells arrested in the G2/M phase after exposure to $PM_{2.5}$, and this occurred through up-regulation of p53 and p21 and down-regulation of CDK1 expression [98]. $PM_{2.5}$ also has profound effects on the expression of miRNAs. Ning et al. [99] found 13 deregulated miRNAs related to lung cancer in the serum of mice inhaled $PM_{2.5}$ for 8 weeks. Moreover, miR-32, miR-582–5p, and miR-199a-5p participate in $PM_{2.5}$-induced EMT and CSC processes, suggesting that miRNAs might be potential targets for lung cancer therapy [94,95,100]. We found that melatonin has an anti-tumor effect by reducing oxidative damage [101]. Further research on the role of melatonin in lung cancer cells exposure to $PM_{2.5}$ may be beneficial to the treatment of $PM_{2.5}$-related lung cancer.

Changes in the lung cancer micro-environment, including inflammatory cytokines, inflammatory cells, and angiogenesis, are associated with $PM_{2.5}$-induced tumor progression and metastasis. The proliferation and motility of tumor cells were significantly enhanced under $PM_{2.5}$ stimulation in which IL-1β and MMP-1 appeared to regulate the process [102]. The expression of IL-17a was increased in NSCLC patients. Long-term exposure to $PM_{2.5}$ significantly up-regulated IL-17a in mice, resulting in increased expression of TGF-β1 and its downstream signal, such as MMP-2 and MMP-9. These accelerated EMT and promoted the development of NSCLC [88]. $PM_{2.5}$ stimulates $CD4^+$ and $CD8^+$ T cells to release IFN-γ, IL-17, and IL-21, and effectively induces cell death in cultured HBECs. Of note, this process occurs in a macrophage-dependent manner, eventually damaging the respiratory tract and promoting the progression of lung cancer [103]. Vascular endothelial growth factor (VEGF) plays a crucial role in the maturation and remodeling of tumor blood vessels. A study revealed that $PM_{2.5}$ exposure recruited macrophages, induced angiogenesis by secreting VEGF, and enhanced the invasion and infiltration of lung cancer both in vivo and in vitro [104].

3. Conclusions

Despite many countries have strengthened the governance of air pollution in recent years, the reduction of environmental $PM_{2.5}$ remains a major challenge. This is associated with the continuous rise of the morbidity and mortality of many diseases. Understanding the impact of $PM_{2.5}$ on common chronic airway diseases would be the first step towards prevention and diagnosis of the health problems caused by $PM_{2.5}$. Due to differences in $PM_{2.5}$ composition and concentration in different countries and regions, it is necessary to conduct multi-regional cooperative research in the future to help reduce the significant health burden.

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