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

Xin Li and Xiaoju Liu *

Department of Gerontal Respiratory Medicine, The First Hospital of Lanzhou University, Lanzhou 730000, China; lix20@lzu.edu.cn
* Correspondence: liuxiaoju835@126.com or liuxj@lzu.edu.cn

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

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). 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 (−8.33 mL [95% CI: −92.50, −73.75]) and FVC (−62.62 mL [95% CI: −73.91, −51.32]). |
| Doiron et al., 2019 [7] | UK          | 303,887           | COPD prevalence and lung function | 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 [6] | Mexico  | 29                | COPD symptoms | Per 10 µg/m$^3$ increase in PM$_{2.5}$ was positively correlated with 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). The hazard ratio (HR) of per 5.3 µg/m$^3$ increase in PM$_{2.5}$ for lung cancer incidence was 1.02 (95% CI: 1.01–1.05) |
| Bai et al., 2019 [14]  | Canada      | 100,146           | lung cancer prevalence | |

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$^3$ increase 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 µg/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 µg/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 µg/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.](image)

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 µg/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 µg/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 µg/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 neutrophil 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-β 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.

Author Contributions: Writing, X.L. (Xin Li); Supervision, X.L. (Xiaoju Liu). All authors have read and agreed to the published version of the manuscript.
Funding: This research was funded by National Natural Science Foundation of China (Grant 81670033, 81960009).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. World Health Organization. Air Pollution. Available online: https://www.who.int/health-topics/air-pollution#tab=tab_1 (accessed on 5 July 2021).
2. Lancet, T. WHO’s global air-quality guidelines. Lancet 2006, 368, 1302. [CrossRef]
3. Collaborators, G.B. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990–2015: A systematic analysis for the Global Burden of Disease Study 2015. Lancet 2016, 388, 1659–1724. [CrossRef]
4. Moller, W.; Felten, K.; Sommerer, K.; Scheuch, G.; Meyer, G.; Meyer, P.; Haussinger, K.; Kreyling, W.G. Deposition, retention, and translocation of ultrafine particles from the central airways and lung periphery. Am. J. Respir. Crit. Care Med. 2008, 177, 426–432. [CrossRef]
5. Pun, V.C.; Kazemiparkouhi, F.; Manjourides, J.; Suh, H.H. Long-Term PM2.5 Exposure and Respiratory, Cancer, and Cardiovascular Mortality in Older US Adults. Am. J. Epidemiol. 2017, 186, 961–969. [CrossRef] [PubMed]
6. Dong, J.; Liu, Y.; Bao, H. Revalue associations of short-term exposure to air pollution with respiratory hospital admissions in Lanzhou, China after the control and treatment of current pollution. Int. J. Hyg. Environ. Health 2021, 231, 113658. [CrossRef] [PubMed]
7. Doiron, D.; de Hoogh, K.; Probst-Hensch, N.; Fortier, I.; Cai, Y.; De Matteis, S.; Hansell, A.L. Air pollution, lung function and COPD: Results from the population-based UK Biobank study. Eur. Respir. J. 2019, 54, 1802140. [CrossRef]
8. Cortez-Lugo, M.; Ramirez-Aguilar, M.; Perez-Padilla, R.; Sansores-Martinez, R.; Ramirez-Venegas, A.; Barraza-Villarreal, A. Effect of Personal Exposure to PM2.5 on Respiratory Health in a Mexican Panel of Patients with COPD. Int. J. Environ. Res. Public Health 2015, 12, 10635–10647. [CrossRef] [PubMed]
9. Bao, H.; Dong, J.; Liu, X.; Tan, E.; Shu, J.; Li, S. Association between ambient particulate matter and hospital outpatient visits for chronic obstructive pulmonary disease in Lanzhou, China. Environ. Sci. Pollut. Res. Int. 2020, 27, 22843–22854. [CrossRef]
10. Chi, R.; Li, H.; Wang, Q.; Zhai, Q.; Wang, D.; Wu, M.; Liu, Q.; Wu, S.; Ma, Q.; Deng, F.; et al. Association of emergency room visits for respiratory diseases with sources of ambient PM2.5. J. Environ. Sci. 2019, 86, 154–163. [CrossRef]
11. Dunea, D.; Iordache, S.; Pohoata, A. Fine Particulate Matter in Urban Environments: A Trigger of Respiratory Symptoms in Sensitive Children. Int. J. Environ. Res. Public Health 2016, 13, 1246. [CrossRef]
12. Hazlehurst, M.F.; Carroll, K.N.; Loftus, C.T.; Szpiro, A.A.; Moore, P.E.; Kaufman, J.D.; Kirwa, K.; LeWinn, K.Z.; Bush, N.R.; Sathyarayananaya, S.; et al. Maternal exposure to PM2.5 during pregnancy and asthma risk in early childhood: Consideration of phases of fetal lung development. Environ. Epidemiol. 2021, 5, e130. [CrossRef]
13. Abdul Wahab, S.; Hassan, A.; Latif, M.T.; Vadeveel, Y.; Yeyabalan, T.; Soo, C.J.; Abdul Hamid, F.; Yu-Lin, A.B.; Hassan, T. Cluster Analysis Evaluating PM2.5, Occupation Risk and Mode of Transportation as Surrogates for Air-pollution and the Impact on Lung Cancer Diagnosis and 1-Year Mortality. Asian Pac. J. Cancer Prev. 2019, 20, 1959–1965. [CrossRef] [PubMed]
14. Bai, L.; Shin, S.; Burnett, R.T.; Kwong, J.C.; Hystad, P.; van Donkelaar, A.; Goldberg, M.S.; Lavigne, E.; Weichenthal, S.; Martin, R.V.; et al. Exposure to ambient air pollution and the incidence of lung cancer and breast cancer in the Ontario Population Health and Environment Cohort. Int. J. Cancer 2020, 146, 2450–2459. [CrossRef] [PubMed]
15. Burney, P.G.; Patel, J.; Newson, R.; Minelli, C.; Naghavi, M. Global and regional trends in COPD mortality, 1990–2010. Eur. Respir. J. 2015, 45, 1239–1247. [CrossRef]
16. Heinrich, J.; Schikowski, T. COPD Patients as Vulnerable Subpopulation for Exposure to Ambient Air Pollution. Curr. Environ. Health Rep. 2018, 5, 70–76. [CrossRef]
17. Duan, R.; Niu, H.; Yu, T.; Huang, K.; Cui, H.; Chen, C.; Yang, T.; Wang, C. Adverse effects of short-term personal exposure to fine particulate matter on the lung function of patients with chronic obstructive pulmonary disease and asthma: A longitudinal panel study in Beijing, China. Environ. Sci. Pollut. Res. Int. 2021. [CrossRef] [PubMed]
18. Lin, C.Y.; Li, D.; Lu, J.M.; Yu, Z.B.; Zhu, Y.; Shen, P.; Tang, M.L.; Jin, M.J.; Lin, H.B.; Shui, L.M.; et al. Short-term associations between ambient fine particulate matter pollution and hospital visits for chronic obstructive pulmonary disease in Yinzhou District, China. Environ. Sci. Pollut. Res. Int. 2020, 27, 21647–21653. [CrossRef]
19. Wang, K.; Hao, Y.; Au, W.; Christiani, D.C.; Xia, Z.L. A Systematic Review and Meta-Analysis on Short-Term Particulate Matter Exposure and Chronic Obstructive Pulmonary Disease Hospitalizations in China. J. Occup. Environ. Med. 2019, 61, e112–e124. [CrossRef]
20. Jo, Y.S.; Lim, M.N.; Han, Y.J.; Kim, W.J. Epidemiological study of PM2.5 and risk of COPD-related hospital visits in association with particle constituents in Chuncheon, Korea. Int. J. Chron. Obstruct. Pulmon. Dis. 2018, 13, 299–307. [CrossRef]
21. Pini, L.; Giordani, J.; Gardini, G.; Concoreggi, C.; Pini, A.; Perger, E.; Vizzardi, E.; Di Bona, D.; Cappelli, C.; Ciarfalglia, M.; et al. Emergency department admission and hospitalization for COPD exacerbation and particulate matter short-term exposure in Brescia, a highly polluted town in northern Italy. *Respir. Med.* 2021, 179, 106334. [CrossRef]

22. Li, M.H.; Fan, L.C.; Mao, B.; Yang, J.W.; Choi, A.M.; Cao, W.J.; Xu, J.F. Short-term Exposure to Ambient Fine Particulate Matter Increases Hospitalizations and Mortality in COPD: A Systematic Review and Meta-analysis. *Chest* 2016, 149, 447–458. [CrossRef] [PubMed]

23. Hwang, S.L.; Guo, S.E.; Chi, M.C.; Chou, C.T.; Lin, Y.C.; Lin, C.M.; Chou, Y.L. Association between Atmospheric Fine Particulate Matter and Hospital Admissions for Chronic Obstructive Pulmonary Disease in Southwestern Taiwan: A Population-Based Study. *Int. J. Environ. Res. Public Health* 2016, 13, 366. [CrossRef]

24. Samoli, E.; Stafoggia, M.; Rodopoulou, S.; Ostro, B.; Alessandrini, E.; Basagana, X.; Diaz, J.; Faustini, A.; Gandini, M.; Karanasiou, A.; et al. Which specific causes of death are associated with short term exposure to fine and coarse particles in Southern Europe? Results from the MED-PARTICLES project. *Environ. Int.* 2014, 67, 54–61. [CrossRef] [PubMed]

25. Alexeeff, S.E.; Deosaransingh, K.; Liao, N.S.; Van Den Eeden, S.K.; Schwartz, J.; Sidney, S. Particulate Matter and Cardiovascular Risk in Adults with Chronic Obstructive Pulmonary Disease. *Am. J. Respir. Crit. Care Med.* 2021, 204, 159–167. [CrossRef] [PubMed]

26. Gan, W.Q.; FitzGerald, J.M.; Carlsten, C.; Sadatsafavi, M.; Brauer, M. Associations of ambient air pollution with chronic obstructive pulmonary disease hospitalization and mortality. *Am. J. Respir. Crit. Care Med.* 2013, 187, 721–727. [CrossRef] [PubMed]

27. Uccelli, R.; Mastrantonio, M.; Altavista, P.; Pacchierotti, F.; Piersanti, A.; Giancarella, L. Impact of modelled PM2.5, NO2 and O3 annual air concentrations on some causes of mortality in Tuscany municipalities. *Eur. J. Public Health* 2019, 29, 871–876. [CrossRef]

28. Jia, H.; Liu, Y.; Guo, D.; He, W.; Zhao, L.; Xia, S. PM2.5-induced pulmonary inflammation via activating of the NLRP3/caspase-1 signaling pathway. *Environ. Toxicol.* 2021, 36, 298–307. [CrossRef] [PubMed]

29. Zhao, J.; Li, M.; Wang, Z.; Chen, J.; Zhao, J.; Xu, Y.; Wei, X.; Wang, J.; Xie, J. Role of PM2.5 in the development and progression of COPD and its mechanisms. *Respir. Res.* 2019, 20, 120. [CrossRef]

30. Zhao, Q.; Chen, H.; Yang, T.; Rui, W.; Liu, F.; Zhang, F.; Zhao, Y.; Ding, W. Direct effects of airborne PM2.5 exposure on macrophage polarizations. *Biochim. Biophys. Acta* 2016, 1860, 2835–2843. [CrossRef]

31. Xu, F.; Xu, A.; Guo, Y.; Bai, Q.; Wu, X.; Ji, S.P.; Xia, R.X. PM2.5 exposure induces alveolar epithelial cell apoptosis and causes emphysema through p53/Siva-1. *Eur. Rev. Med. Pharmacol. Sci.* 2020, 24, 3943–3950. [CrossRef]

32. Wang, J.; Li, Y.; Zhao, P.; Tian, Y.; Liu, X.; He, H.; Jia, R.; Oliver, B.G.; Li, J. Exposure to Air Pollution Exacerbates Inflammation in Rats with Preexisting COPD. *Mediat. Inflamm.* 2020, 2020, 4260204. [CrossRef] [PubMed]

33. Zhao, Q.J.; Liu, X.J.; Zeng, X.L.; Bao, H.R. Effect of PM2.5 on the level of nuclear factor erythroid-2 related factor 2 in chronic obstructive pulmonary disease mice and its relationship with oxidative stress. *Zhonghua Yi Xue Za Zhi* 2016, 96, 2241–2245. [CrossRef] [PubMed]

34. Chu, X.; Liu, X.J.; Qiu, J.M.; Zeng, X.L.; Bao, H.R. Inhibitory effects of codonopsis pilosula polysaccharides on the deterioration of impaired phagocytosis of alveolar macrophage induced by fine particulate matter in chronic obstructive pulmonary disease mice. *Zhonghua Yi Xue Za Zhi* 2016, 96, 1134–1138. [CrossRef]

35. Gu, X.Y.; Chu, X.; Zeng, X.L.; Bao, H.R.; Liu, X.J. Effects of PM2.5 exposure on the Notch signaling pathway and immune imbalance in chronic obstructive pulmonary disease patients. *Zhonghua Yi Xue Za Zhi* 2014, 94, 895–898. [PubMed]

36. He, M.; Ichinose, T.; Yoshida, S.; Ito, T.; He, C.; Yoshida, Y.; Arashidani, K.; Takano, H.; Sun, G.; Shibamoto, T. PM2.5-induced lung inflammation in mice: Differences of inflammatory response in macrophages and type II alveolar cells. *J. Appl. Toxicol.* 2017, 37, 1203–1218. [CrossRef]

37. Zeng, X.; Liu, X.; Bao, H. Sulforaphane suppresses lipopolysaccharide- and Pam3CysSerLys4-mediated inflammation in chronic obstructive pulmonary disease via toll-like receptors. *FEBS Open Bio* 2021, 11, 1313–1321. [CrossRef] [PubMed]

38. Pang, Q.; Liu, X.; Shi, K.; Zeng, X.; Bao, H. Effects of cigarette smoke on phagocytosed function of monocyte-derived macrophage in chronic obstructive pulmonary disease patients. *Zonghua Yi Xue Za Zhi* 2014, 94, 895–898. [PubMed]

39. Chu, X.; Liu, X.J.; Qiu, J.M.; Zeng, X.L.; Bao, H.R.; Shu, J. Effects of Astragalus and Codonopsis pilosula polysaccharides on alveolar macrophage phagocytosis and inflammation in chronic obstructive pulmonary disease mice exposed to PM2.5. *Environ. Toxicol. Pharmacol.* 2016, 48, 76–84. [CrossRef] [PubMed]

40. Shu, J.; Liu, X.; Chu, X.; Qiu, J.; Zeng, X.; Bao, H. Effects of PM2.5 on phagocytic function of alveolar macrophages in chronic obstructive pulmonary disease mice. *Zhonghua Yi Xue Za Zhi* 2016, 96, 301–305. [CrossRef] [PubMed]

41. Huo, S.J.; Hu, Y.; Zeng, X.L.; Bao, H.R.; Liu, X.J. The effect of fine particles on the phagocytosis of alveolar macrophages potentially by Arp2/3 complex in a mouse model of chronic obstructive pulmonary disease. *Zhonghua Jie He He Hu Xi Za Zhi* 2019, 42, 907–915. [CrossRef] [PubMed]

42. Xia, Q.; Hu, S.T.; Zeng, X.L.; Bao, H.R.; Liu, X.J. Mechanisms of cytoskeleton and PI3KDelta-RhoA in fine particulate matter deteriorating phagocytosis defect of alveolar macrophage in mice with chronic obstructive pulmonary disease. *Zhonghua Yi Xue Za Zhi* 2017, 97, 1893–1898. [CrossRef] [PubMed]

43. Jiang, Y.; Zhao, Y.; Wang, Q.; Chen, H.; Zhou, X. Fine particulate matter exposure promotes M2 macrophage polarization through inhibiting histone deacetylase 2 in the pathogenesis of chronic obstructive pulmonary disease. *Ann. Transl. Med.* 2020, 8, 1303. [CrossRef]
44. Zou, W.; Wang, X.; Hong, W.; He, F.; Hu, J.; Sheng, Q.; Zhu, T.; Ran, P. PM2.5 Induces the Expression of Inflammatory Cytokines via the Wnt5a/Ror2 Pathway in Human Bronchial Epithelial Cells. *Int. J. Chron. Obstruct. Pulmon. Dis.* 2020, 15, 2653–2662. [CrossRef] [PubMed]

45. Deng, X.; Zhang, F.; Rui, W.; Long, F.; Wang, L.; Feng, Z.; Chen, D.; Ding, W. PM2.5-induced oxidative stress triggers autophagy in human lung alveolar epithelial A549 cells. *Toxicol. In Vitro* 2013, 27, 1762–1770. [CrossRef]

46. Zhu, X.M.; Wang, Q.; Xing, W.W.; Long, M.H.; Fu, W.L.; Xia, W.R.; Jin, C.; Guo, N.; Xu, D.Q.; Xu, D.G. PM2.5 induces autophagy-mediated cell death via NO82 signaling in human bronchial epithelium cells. *Int. J. Biol. Sci.* 2018, 14, 557–564. [CrossRef] [PubMed]

47. Jin, X.; Xue, B.; Zhou, Q.; Su, R.; Li, Z. Mitochondrial damage mediated by ROS incurs bronchial epithelial cell apoptosis upon ambient PM2.5 exposure. *J. Toxicol. Sci.* 2018, 43, 101–111. [CrossRef] [PubMed]

48. Li, J.; Zhou, Q.; Liang, Y.; Pan, W.; Bei, Y.; Zhang, Y.; Wang, J.; Jiao, Z. miR-486 inhibits PM2.5-induced apoptosis and oxidative stress in human lung alveolar epithelial A549 cells. *Ann. Transl. Med.* 2016, 6, 209. [CrossRef]

49. Li, X.; Zheng, M.; Pu, J.; Zhou, Y.; Hong, W.; Fu, X.; Peng, Y.; Zhou, W.; Fan, H.; Li, B.; et al. Identification of abnormally expressed IncRNAs induced by PM2.5 in human bronchial epithelial cells. *Biosci. Rep.* 2018, 38, BSR20171577. [CrossRef]

50. Hirose, K.; Iwata, A.; Tamachi, T.; Nakajima, H. Allergic airway inflammation: Key players beyond the Th2 cell pathway. *Immunol. Rev.* 2017, 278, 145–161. [CrossRef]

51. Huo, Y.; Zhang, H.Y. Genetic Mechanisms of Asthma and the Implications for Drug Repositioning. *Genes* 2018, 9, 237. [CrossRef]

52. Godri Pollitt, K.J.; Maikawa, C.L.; Wheeler, A.J.; Weichenthal, S.; Dobbin, N.A.; Liu, L.; Goldberg, M.S. Trace metal exposure is associated with increased exhaled nitric oxide in asthmatic children. *Environ. Health* 2016, 15, 94. [CrossRef]

53. Qibin, L.; Yacan, L.; Minli, J.; Meixi, Z.; Chengye, L.; Yuping, L.; Chang, C. The impact of PM2.5 on lung function in adults with asthma. *Int. J. Tuberc. Lung Dis.* 2020, 24, 570–576. [CrossRef] [PubMed]

54. Fan, J.; Li, S.; Fan, C.; Bai, Z.; Yang, K. The impact of PM2.5 on asthma emergency department visits: A systematic review and meta-analysis. *Environ. Sci. Pollut. Res. Int.* 2016, 23, 843–850. [CrossRef] [PubMed]

55. Anenberg, S.C.; Henze, D.K.; Tinney, V.; Kinney, P.L.; Raich, W.; Fann, N.; Malley, C.S.; Roman, H.; Lamsal, L.; Duncan, B.; et al. Estimates of the Global Burden of Ambient PM2.5, Ozone, and NO2 on Asthma Incidence and Emergency Room Visits. *Environ. Health Perspect.* 2018, 126, 107004. [CrossRef]

56. Bouzza, N.; Foissac, F.; Urrien, S.; Guedj, R.; Carbajal, R.; Treluyer, J.M.; Chappuy, H. Fine particulate pollution and asthma exacerbations. *Arch. Dis. Child.* 2018, 103, 828–831. [CrossRef] [PubMed]

57. Huo, Y.; Zhang, H.Y. Genetic Mechanisms of Asthma and the Implications for Drug Repositioning. *Genes* 2018, 9, 237. [CrossRef]

58. Garcia, E.; Berhane, K.T.; Islam, T.; Weichenthal, S.; Dobbin, N.A.; Liu, L.; Goldberg, M.S. Trace metal exposure is associated with increased exhaled nitric oxide in asthmatic children. *Environ. Health* 2016, 15, 94. [CrossRef]

59. Huo, Y.; Zhang, H.Y. Genetic Mechanisms of Asthma and the Implications for Drug Repositioning. *Genes* 2018, 9, 237. [CrossRef]

60. Bowatte, G.; Lodge, C.; Lowe, A.J.; Erbas, B.; Perret, J.; Abramson, M.J.; Matheson, M.; Dharmage, S.C. The influence of childhood traffic-related air pollution exposure on asthma, allergy and sensitization: A systematic review and a meta-analysis of birth cohort studies. *Allergy* 2015, 70, 245–256. [CrossRef]

61. Garcia, E.; Berhane, K.T.; Islam, T.; McConnell, R.; Urman, R.; Chen, Z.; Gilliland, F.D. Association of Changes in Air Quality With Incident Asthma in Children in California, 1993–2014. *JAMA* 2019, 321, 1906–1915. [CrossRef]

62. Pennington, A.F.; Strickland, M.J.; Klein, M.; Zhai, X.; Bates, J.T.; Drews-Botsch, C.; Hansen, C.; Russell, A.G.; Tolbert, P.E.; Darrow, L.A. Exposure to Mobile Source Air Pollution in Early-life and Childhood Asthma Incidence: The Kaiser Air Pollution and Pediatric Asthma Study. *Epidemiology* 2018, 29, 22–30. [CrossRef] [PubMed]

63. Bao, Z.L.; Fan, Y.M.; Cui, Y.F.; Sheng, Y.F.; Zhu, M. Effect of PM2.5 mediated oxidative stress on the innate immune cellular response of Der p1 treated human bronchial epithelial cells. *Eur. Rev. Med. Pharmacol. Sci.* 2017, 21, 2907–2912.
70. Pang, L.; Zou, S.; Shi, Y.; Mao, Q.; Chen, Y. Apigenin attenuates PM2.5-induced airway hyperresponsiveness and inflammation by down-regulating NF-kappaB in murine model of asthma. *Int. J. Clin. Exp. Pathol*. 2019, 12, 3700–3709.

71. He, Z.; Wu, J.; Zeng, X.; Bao, H.; Liu, X. Role of the Notch ligands Jagged1 and Delta4 in Th17/Treg immune imbalance in a mouse model of chronic asthma. *Exp. Lung Res*. 2021, 47, 289–299. [CrossRef]

72. Sun, L.; Fu, J.; Lin, S.H.; Sun, J.L.; Xia, L.; Lin, C.H.; Liu, L.; Zhang, C.; Yang, L.; Xue, P.; et al. Particulate matter of 2.5 mum or less in diameter disturbs the balance of TH17/regulatory T cells by targeting glutamate oxaloacetate transaminase 1 and hypoaxia-inducing factor alpha in an asthma model. *J. Allergy Clin. Immunol*. 2020, 145, 402–414. [CrossRef]

73. Yang, Y.; Li, X.; An, X.; Zhang, L.; Li, X.; Wang, L.; Zhu, G. Continuous exposure of PM2.5 exaggerates ovalbumin-induced asthma in mouse lung via a JAK-STAT6 signaling pathway. *Asthma. Clin. Exp. Med*. 2020, 29, 825–832. [CrossRef]

74. He, M.; Ichinose, T.; Yoshida, Y.; Arashidani, K.; Yoshida, S.; Takano, H.; Sun, G.; Shibamoto, T. Urban PM2.5 exaggerates allergic inflammation in the murine lung via a TLR2/TLR4/MyD88-signaling pathway. *Sci. Rep*. 2017, 7, 11027. [CrossRef] [PubMed]

75. Zhang, J.; Zeng, X.; Li, Y.; Zhao, W.; Chen, Z.; Du, Q.; Zhou, F.; Ji, N.; Huang, M. Exposure to Ambient Particles Alters the Evolution of Macrophage Phenotype and Amplifies the Inducible Release of Eotaxin-1 in Allergen-Sensitized Mice. *J. Biomed. Nanotechnol*. 2019, 15, 382–395. [CrossRef] [PubMed]

76. Zhang, L.; Fulgar, C.C.; Mar, T.; Young, D.E.; Zhang, Q.; Bein, K.J.; Cui, L.; Castaneda, A.; Vogel, C.F.; Sun, X.; et al. TH17-Induced Neutrophils Enhance the Pulmonary Allergic Response Following BALB/c Exposure to House Dust Mite Allergen and Fine Particulate Matter from California and China. *Toxicol. Sci*. 2018, 164, 627–643. [CrossRef]

77. Yu, P.F.; Pang, L.L.; Mao, Q.S.; Shi, Y.; Lin, D.J. Dose dependency PM2.5 aggravated airway inflammation in asthmatic mice via down-regulating expression of ITGB4. *Eur. Rev. Med. Pharmacol. Sci*. 2019, 23, 1688–1697. [CrossRef] [PubMed]

78. He, X.; Zhang, L.; Xiong, A.; Ran, Q.; Wang, J.; Wu, D.; Niu, B.; Liu, S.; Li, G. PM2.5 aggravates NQO1-induced mucus hypersecretion through release of neutrophil extracellular traps in an asthma model. *Ecotoxicol. Environ. Saf*. 2021, 218, 112272. [CrossRef] [PubMed]

79. Zhao, C.; Wang, Y.; Su, Z.; Pu, W.; Niu, M.; Song, S.; Wei, L.; Ding, Y.; Xu, L.; Tian, M.; et al. Respiratory exposure to PM2.5 soluble extract disrupts mucosal barrier function and promotes the development of experimental asthma. *Sci. Total Environ.* 2020, 730, 139145. [CrossRef]

80. Loomis, D.; Gross, Y.; Lauby-Secretan, B.; El Ghissassi, F.; Bouvard, V.; Benbrahim-Tallae, L.; Guha, N.; Baan, R.; Mattock, H.; Straif, K.; et al. The carcinogenicity of outdoor air pollution. *Lancet Oncol*. 2013, 14, 1262–1263. [CrossRef]

81. Guo, H.; Li, W.; Wu, J. Ambient PM2.5 and Annual Lung Cancer Incidence: A Nationwide Study in 295 Chinese Counties. *Int. J. Environ. Res. Public Health* 2020, 17, 1481. [CrossRef] [PubMed]

82. Huang, F.; Pan, B.; Wu, J.; Chen, E.; Chen, L. Relationship between exposure to PM2.5 and lung cancer incidence and mortality: A meta-analysis. *Oncotarget* 2017, 8, 43322–43331. [CrossRef] [PubMed]

83. Yang, D.; Liu, Y.; Bai, C.; Wang, X.; Powell, C.A. Epidemiology of lung cancer and lung cancer screening programs in China and the United States. *Cancer*. 2020, 468, 82–87. [CrossRef]

84. Tomczak, A.; Miller, A.B.; Weichert, M.A.; To, T.; Wall, C.; van Donkelaar, A.; Martin, R.V.; Crouse, D.L.; Villeneuve, P.J. Long-term exposure to fine particulate matter air pollution and the risk of lung cancer among participants of the Canadian National Breast Screening Study. *Int. J. Cancer* 2016, 139, 1958–1966. [CrossRef] [PubMed]

85. Nieuwenhuijsen, M.J.; Brunekreef, B.; et al. Air pollution and lung cancer incidence in 17 European cohorts: Prospective analyses from the European Study of Cohorts for Air Pollution Effects (ESCAPE). *Lancet Oncol*. 2013, 14, 813–822. [CrossRef]

86. Wu, X.; Zhu, B.; Zhou, J.; Bi, Y.; Xu, S.; Zhou, B. The epidemiological trends in the burden of lung cancer attributable to PM2.5 exposure in China. *BMC Public Health* 2021, 21, 737. [CrossRef]

87. Chao, X.; Li, Y.; Lan, L.L.; Wei, H.Y.; Wei, D. Long-term PM2.5 exposure increases the risk of non-small cell lung cancer (NSCLC) progression by enhancing interleukin-17a (IL-17a)-regulated proliferation and metastasis. *Aging* 2020, 12, 11579–11602. [CrossRef]

88. Chen, Z.; Ji, N.; Wang, Z.; Wu, C.; Sun, Z.; Li, Y.; Hu, F.; Wang, Z.; Huang, M.; Zhang, M. Fine Particulate Matter (PM2.5) Promoted the Invasion of Lung Cancer Cells via an ARNT2/PP2A/STAT3/MMP2 Pathway. *J. Biomed. Nanotechnol*. 2018, 14, 2172–2184. [CrossRef]

89. Tian, L.; Li, Y.; Liu, H.L.; Lai, W.Q.; Shi, Y.; Liu, X.H.; Xi, Z.G.; Lin, B.C. Exposure to PM2.5 Enhances the PI3K/AKT Signaling and Malignancy of ERalpha Expression-dependent Non-small Cell Lung Carcinoma. *Biomed. Environ. Sci*. 2021, 34, 319–323. [CrossRef]

90. Lin, H.; Zhang, X.; Feng, N.; Wang, R.; Zhang, W.; Deng, X.; Wang, Y.; Yu, X.; Ye, X.; Li, L.; et al. LncRNA LCPAT1 Mediates Smoking/Particulate Matter 2.5-Induced Cell Autophagy and Epithelial-Mesenchymal Transition in Lung Cancer Cells via RCC2. *Cell Physiol. Biochem.* 2018, 47, 1244–1258. [CrossRef]

91. Wang, Y.; Zhong, Y.; Hou, T.; Liao, J.; Zhang, C.; Sun, C.; Wang, G. PM2.5 induces EMT and promotes CSC properties by activating Notch pathway in vivo and vitro. *Ecotoxicol. Environ. Saf*. 2019, 178, 159–167. [CrossRef] [PubMed]

92. Wang, Y.; Zhong, Y.; Sun, K.; Fan, Y.; Liao, J.; Wang, G. Identification of exosome miRNAs in bronchial epithelial cells after PM2.5 chronic exposure. *Ecotoxicol. Environ. Saf*. 2021, 215, 112127. [CrossRef]
94. Jiang, P.; Hao, S.; Xie, L.; Xiang, G.; Hu, W.; Wu, Q.; Liu, Z.; Li, S. LncRNA NEAT1 contributes to the acquisition of a tumor like-phenotype induced by PM 2.5 in lung bronchial epithelial cells via HIF-1alpha activation. *Environ. Sci. Pollut. Res. Int.* 2021, 28, 43382–43393. [CrossRef] [PubMed]

95. Yang, D.; Ma, M.; Zhou, W.; Yang, B.; Xiao, C. Inhibition of miR-32 activity promoted EMT induced by PM2.5 exposure through the modulation of the Smad1-mediated signaling pathways in lung cancer cells. *Chemosphere* 2017, 184, 289–298. [CrossRef] [PubMed]

96. Yang, B.; Li, X.; Chen, D.; Xiao, C. Effects of fine air particulates on gene expression in non-small-cell lung cancer. *Adv. Med. Sci.* 2017, 62, 295–301. [CrossRef] [PubMed]

97. Zhou, W.; Tian, D.; He, J.; Wang, Y.; Zhang, L.; Cui, L.; Jia, L.; Zhang, L.; Li, L.; Shu, Y.; et al. Repeated PM2.5 exposure inhibits BEAS-2B cell P53 expression through ROS-Akt-DNMT3B pathway-mediated promoter hypermethylation. *Oncotarget* 2016, 7, 20691–20703. [CrossRef]

98. Yang, J.; Huo, T.; Zhang, X.; Ma, J.; Wang, Y.; Dong, F.; Deng, J. Oxidative stress and cell cycle arrest induced by short-term exposure to dustfall PM2.5 in A549 cells. *Environ. Sci. Pollut. Res. Int.* 2018, 25, 22408–22419. [CrossRef]

99. Ning, J.; Li, P.; Zhang, B.; Han, B.; Su, X.; Wang, Q.; Wang, X.; Li, B.; Kang, H.; Zhou, L.; et al. miRNAs deregulation in serum of mice is associated with lung cancer related pathway deregulation induced by PM2.5. *Environ. Pollut.* 2019, 254, 112875. [CrossRef]

100. Qi, H.; Liu, Y.; Wang, N.; Xiao, C. Lentinan Attenuated the PM2.5 Exposure-Induced Inflammatory Response, Epithelial-Mesenchymal Transition and Migration by Inhibiting the PVT1/miR-199a-5p/caveolin1 Pathway in Lung Cancer. *DNA Cell Biol.* 2021, 40, 683–693. [CrossRef]

101. Liu, X.; Zhao, J.; Zheng, R. DNA damage of tumor-associated lymphocytes and total antioxidant capacity in cancerous patients. *Mutat. Res.* 2003, 539, 1–8. [CrossRef]

102. Yang, B.; Chen, D.; Zhao, H.; Xiao, C. The effects for PM2.5 exposure on non-small-cell lung cancer induced motility and proliferation. *Springerplus* 2016, 5, 2059. [CrossRef]

103. Ma, Q.Y.; Huang, D.Y.; Zhang, H.J.; Wang, S.; Chen, X.F. Exposure to particulate matter 2.5 (PM2.5) induced macrophage-dependent inflammation, characterized by increased Th1/Th17 cytokine secretion and cytotoxicity. *Int. Immunopharmacol.* 2017, 50, 139–145. [CrossRef] [PubMed]

104. Li, R.; Yang, L.; Jiang, N.; Wang, F.; Zhang, P.; Zhou, R.; Zhang, J. Activated macrophages are crucial during acute PM2.5 exposure-induced angiogenesis in lung cancer. *Oncol. Lett.* 2020, 19, 725–734. [CrossRef]