Function of PM2.5 in the pathogenesis of lung cancer and chronic airway inflammatory diseases (Review)

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Abstract. Previous research has identified that air pollution is associated with various respiratory diseases, but few studies have investigated the function served by particulate matter 2.5 (PM2.5) in these diseases. PM2.5 is known to cause epigenetic and microenvironmental alterations in lung cancer, including tumor-associated signaling pathway activation mediated by microRNA dysregulation, DNA methylation, and increased levels of cytokines and inflammatory cells. Autophagy and apoptosis of tumor cells may also be detected in lung cancer associated with PM2.5 exposure. A number of mechanisms are involved in triggering and aggravating asthma and COPD, including PM2.5-induced cytokine release and oxidative stress. The present review is an overview of the underlying molecular mechanisms of PM2.5-induced pathogenesis in lung cancer and chronic airway inflammatory diseases.

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Contents

1. Introduction
2. PM2.5 has an adverse impact on cardiovascular, respiratory and endocrine systems
3. PM2.5-induced pathogenesis varies in lung cancer
4. PM2.5-induced pathogenesis varies in chronic airway inflammatory diseases
5. PM2.5-induced pathogenesis in lung tuberculosis
6. PM2.5-induced pathogenesis in respiratory infection
7. Conclusions

1. Introduction

Previous studies have identified a marked association between particulate matter 2.5 (PM2.5) exposure and increased incidence of pulmonary diseases (1). PM2.5 is a type of air pollutant with a diameter of ≤ 2.5 μm, characterized by its small particle size (2), large surface area and toxin absorption ability (3). These properties make it possible for PM2.5 to invade the smallest airways, including alveolar tissue. PM2.5 comprises a mixture of solid and liquid particles, including black carbon, metals, nitrate, sulfate, polycyclic aromatic hydrocarbons and automobile exhaust particles (4). It has been demonstrated that exposing mice to PM2.5 led to easier deposition of PM2.5 into lung issues compared with other metal pollutants (5). Numerous biological activities, including cytokine formation, coagulation balance, and cardiac and pulmonary function have been demonstrated to be altered by PM2.5 (6).

It has also been indicated that PM2.5 may trigger asthma, chronic obstructive lung disease (COPD) and lung cancer through the activation of various signaling pathways, including AMP-activated protein kinase (AMPK) catalytic subunit α1 and signal transducer and activator of transcription (STAT)-1 (7). It has also been suggested that vascular endothelial growth factor receptor (VEGF), mitogen-activated protein kinase (MAPK), nuclear factor κB (NF-κB) and interleukin (IL)-8 signaling is involved in PM2.5-induced lung injury (8). In PM2.5-exposed rats, a decrease in phosphatidylcholine levels may be detected, which may impair alveolar type II cells and alter cell functions (9). In addition, PM2.5 exposure has been demonstrated to be associated with endothelial cell

apoptosis and systemic inflammation (10). Numerous studies have suggested that lung function impairment in mice may also be induced by PM2.5 (6), and that the transforming growth factor-β/Smad signaling pathway may participate in this process (11). A European cohort study indicated that PM2.5 exposure increased the risk of lung cancer, particularly lung adenocarcinoma (12). Another study demonstrated that if the daily average concentration of PM2.5 was decreased to 10 μg/m^3, 90% of children with respiratory diseases would be admitted to hospital less frequently (13). Furthermore, each 10-μg/m^3 increase in PM2.5 was indicated to cause a 0.23% increase in total emergency room visits due to respiratory diseases, of which the majority of patients exhibited acute exacerbation of COPD (AECOPD). The rate of respiratory infection has also been demonstrated to increase with increased PM2.5 levels (14). Similar results were obtained in terms of hospital admissions of respiratory diseases and PM2.5 levels in Taiwan (15). Furthermore, it has been revealed that the mortality rates of emphysema, asthma and pneumonia are significantly associated with particulate polluting matter (16). PM2.5 has also been positively associated with the number of outpatient visits for acute respiratory diseases, including acute bronchitis (17).

2. PM2.5 has an adverse impact on cardiovascular, respiratory and endocrine systems

A considerable number of epidemiological studies have demonstrated that long-term exposure to PM2.5 may cause damage to the cardiovascular, respiratory and endocrine systems (18,19). It has been indicated that PM2.5 exposure is associated with a notable proportion of mortalities due to numerous diseases, including lung cancer (23.9%), COPD (18.7%), stroke (40.3%) and ischemic heart disease (IHD) (26.8%) (20). It was reported that each 10-μg/m^3 increase in acute PM2.5 exposure in the northeastern USA resulted in a 0.26% increase in the number of admissions of patients with peripheral artery disease (21). Similarly, in Beijing (China), PM2.5 was significantly associated with the number of hospital emergency room visits for cardiovascular diseases, particularly IHD, heart arrhythmia and atrial fibrillation (22). PM2.5 exposure together with cigarette smoking has been demonstrated to have an even greater impact on cardiovascular disease-associated mortality (23). A meta-analysis study indicated that ambient PM2.5 exposure was associated with a high risk of atrial fibrillation (24). However, it has been reported that lung cancer and cardiovascular diseases respond differently to PM2.5 exposure (25).

In terms of endocrine function, it has been suggested that early-life PM2.5 exposure may serve a pivotal effect in childhood overweight or obesity (26). Another study detected impairment of adult renal function in the Taipei metropolis following exposure to PM10, but not PM2.5 (27).

3. PM2.5-induced pathogenesis varies in lung cancer

Epidemiological studies of lung cancer. Researchers have identified lung cancer as one of the most significant causes of cancer-associated mortality, and non-small cell lung cancer (NSCLC) has been reported to account for 80% lung cancer (28). NSCLC has a low 5-year survival rate (29). Previous epidemiological studies have indicated that ambient PM2.5 is carcinogenic (30), and may increase the morbidity and mortality rates associated with lung cancer (31,32), and PM2.5 has been suggested to decrease the survival time of patients with lung cancer (33). A short-term decrease in PM2.5 exposure has been demonstrated to decrease the population risk of lung cancer (34).

Oncogene activation, mediated by microRNAs (miRs), involved in PM2.5-induced lung cancer. miRs are a class of small non-coding single-stranded RNA molecules which participate in the regulation of post-transcriptional gene expression and RNA silencing (35). It has been established that miRs regulate 50% of protein-coding genes and cell metabolic processes (36). However, the pathogenesis of PM2.5 induction of lung cancer remains to be elucidated. A previous study indicated that exposing human bronchial epithelial (HBE) cells to ambient PM2.5 resulted in down-regulation of miR-182 and miR-185 expression compared with non-exposed cells (37). The expression of three target oncogenes, solute carrier family 30 member 1, serpin family B member 2 and aldo-keto reductase family 1 member C1, which are markedly expressed in human lung adenocarcinoma cells and squamous carcinoma cells, may cause neoplastic transformation in NIH3T3 cells (37). However, whether this is translatable to humans remains unknown. Another study investigated the association between PM2.5 exposure and the miR-802/Rho family GTPase 3 (Rnd3) pathway in lung cancer *in vivo* and *in vitro*. PM2.5 was demonstrated to enhance the growth and metastasis of lung cancer (38). These results warrant further investigation of PM2.5-induced miR changes in lung cancer.

PM2.5-induced gene mutations have been investigated extensively. In one study, following exposure of HBE cells to 200 and 500 μg/ml PM2.5, 970 and 492 gene alterations were detected, respectively (39). Furthermore, an *in vivo* study demonstrated that, in PM2.5-treated mice, 57 genes were demonstrated to be mutated, including 14 upregulated genes and 43 downregulated genes (40). It has been suggested that these mutations occur in response to an exogenous stimulus, metabolic processing and an inflammatory immune pathway, possibly involving the MAPK signaling pathway (41). These studies provide a preliminary basis to direct further investigation of the function of miRs in oncogene activation in lung cancer following PM2.5 exposure. Furthermore, the interaction between PM2.5-induced long non-coding RNA (lncRNA) alteration and lung cancer has been studied, indicating that PM2.5 is able to induce lncRNA loc146880 via reactive oxygen species (ROS), promoting autophagy and malignancy of lung cancer cells (42).

PM2.5-induced tumor suppressor gene inactivation through DNA methylation. p53 is an important regulatory gene in cell proliferation, apoptosis and damage repair (43). Mutation of p53 contributes to the pathogenesis of lung cancer (44,45). A previous study sought to identify PM2.5-induced p53 mutations using human alveolar epithelial BEAS-2B cells constantly exposed to low-dose PM2.5 for 10 days. It was demonstrated that PM2.5 was able to trigger p53 promoter

methylation by increasing DNA (cytosine-5-)-methyltransferase 3β (DNMT3B) methylation levels, resulting in p53 inactivation. The same study indicated that the ROS/protein kinase B (Akt) signaling pathway was involved in the process of DNMT3B methylation (46). Notably, these cells were exposed long term to 'safe' concentrations of PM2.5 (120 μg/m^3). Furthermore, a previous study established that the expression of DNMT was different when cells were acutely exposed to high-dose PM2.5 (data not shown) (46). To the best of our knowledge, inactivation of other PM2.5-induced tumor suppressor genes via DNA methylation has not been demonstrated. However, a recent analysis of the methylome and transcriptome of PM2.5-induced (100 μg/ml) BEAS-2B cells identified 66 differentially expressed genes, which were either hyper- or hypo-methylated, involved in lung diseases, particularly lung cancer (47). A number of the genes were identified to be involved in tumor suppression, including deleted in malignant brain tumors 1, ERBB receptor feedback inhibitor 1 and gap junction protein β2. Another study observed gene methylation in healthy mice exposed to traffic-associated air pollution, including upregulation of p16 and adenomatous polyposis coli methylation, and downregulation of long interspersed nuclear element-1 and nitric oxide synthase 2 methylation (48). It has been demonstrated that following exposure to PM2.5, DNA methylation of tandem repeats increases (49). A tandem repeat (NBL2) methylation has been identified to be associated with PM2.5 silicon in truck drivers, and another tandem repeat (SATα) methylation has been associated with sulfur exposure in office workers (50), which may lead to an increase in the risk of lung cancer. These studies provide a basis for further investigation of the association between PM2.5-induced tumor suppressor gene methylation and lung cancer.

PM2.5-induced microenvironment alteration in lung cancer. The tumor microenvironment is of importance to tumor behavior, particularly in lung cancer (51). The production of cytokines, inflammatory cells and angiogenesis has been identified to be associated with tumor metastasis and tumor cell proliferation (52). Numerous inflammatory cytokines and transcription factors function in the lung cancer tumor microenvironment, including interleukin (IL)-1β and -6, tumor necrosis factor α (TNF-α), NF-κB and STAT-3 (53). PM2.5 exposure is able to increase the mobility and proliferation of A549 and H1299 cells, and IL-1β and MMP-1 may be responsible for the effects of PM2.5 (54). It has also been suggested that alveolar macrophage polarization may serve a function in angiogenesis and tumor growth via secretion of IL-8 and VEGF (55). Previous studies have demonstrated that PM2.5 is able to induce HBE cells and macrophages to release various pro-inflammatory cytokines, including IL-6, TNF-α and granulocyte-macrophage colony stimulating factor (GM-CSF), resulting in airway inflammation (41,56,57). Therefore, by triggering angiogenesis and inflammatory reactions, PM2.5-induced tumor microenvironment alteration may promote tumor growth and metastasis.

PM2.5-induced autophagy and apoptosis. Autophagy refers to the encapsulation of damaged proteins or organelles of eukaryotic cells by autophagic vesicles, followed by lysosomal degradation and recycling (58). Autophagy serves an important function in emergent cell processes, including starvation and infection (59). As a self-destructive activity, apoptosis serves an essential function in tissue homeostasis, embryonic development and organogenesis (60). Crosstalk between autophagic and apoptotic pathways have been characterized in cell fate decision making (61,62). Caspases, a group of cysteine proteases, are best known as apoptosis modulators, and function in the crosstalk between autophagy and apoptosis (63). Crucial autophagy proteins, including Beclin-1 and autophagy-related 5 may be degraded by activated caspases to attenuate the autophagic response (64,65). Furthermore, autophagy is able to regulate apoptosis by altering the level and activity of caspase proteins (66). PM2.5 exposure may induce macrophage autophagy and mediate the Src/STAT-3 signaling pathway to increase the expression of VEGF-A, an important pro-angiogenic factor (67). It has also been suggested that the phosphoinositide 3-kinase/Akt/mechanistic target of rapamycin kinase signaling pathway may serve an important function in the autophagy of BEAS-2B cells exposed to PM2.5 (68). PM2.5 is able to induce autophagy of A549 cells by activating the AMPK signaling pathway (69). Autophagy serves as a protective mechanism, thus preventing further damage by PM2.5 (70).

PM2.5 induces inflammatory cell infiltration and alveolar cell autophagy, and also alters the cell cycle of alveolar epithelial cells and induces cell apoptosis. A number of studies have demonstrated that PM2.5 is able to induce mitotic arrest by breaking DNA double strands and activating the p53/retinoblastoma signaling pathway (71-73). PM2.5 has also been demonstrated to activate the TNF-α signaling pathway and manipulate the transcription of p53, B-cell lymphoma 2 (Bcl-2) and Bcl-2-associated X protein, resulting in apoptosis of alveolar epithelial cells (74,75).

4. PM2.5-induced pathogenesis varies in chronic airway inflammatory diseases

Epidemiological investigation of chronic airway inflammatory diseases. The most common chronic airway inflammatory diseases are asthma and COPD (76). Asthma is characterized by chronic pulmonary inflammation and airway hyper-responsiveness (77). It has been demonstrated that asthma is associated with numerous environmental and genetic factors (78). Epidemiological evidence suggests that air pollution, including ambient PM2.5, may increase the morbidity and hospitalization rate of patients with asthma (79-81). Furthermore, air pollution has become an independent risk factor of asthma (82). Increased PM10 exposure has been identified to be associated with poor control of asthma and poor health-associated quality of life (83). The airway inflammation and immune response in the pathogenesis of asthma have been identified to be associated with the chemical composition and size distribution of PM2.5 (84). It has been identified that with increased levels of the heavy metal lead in PM2.5 in e-waste recycling areas, the level of lead in pediatric blood samples also increased (85). This is a cause for concern since asthma may be induced when blood lead content >5 μg/dl (85).
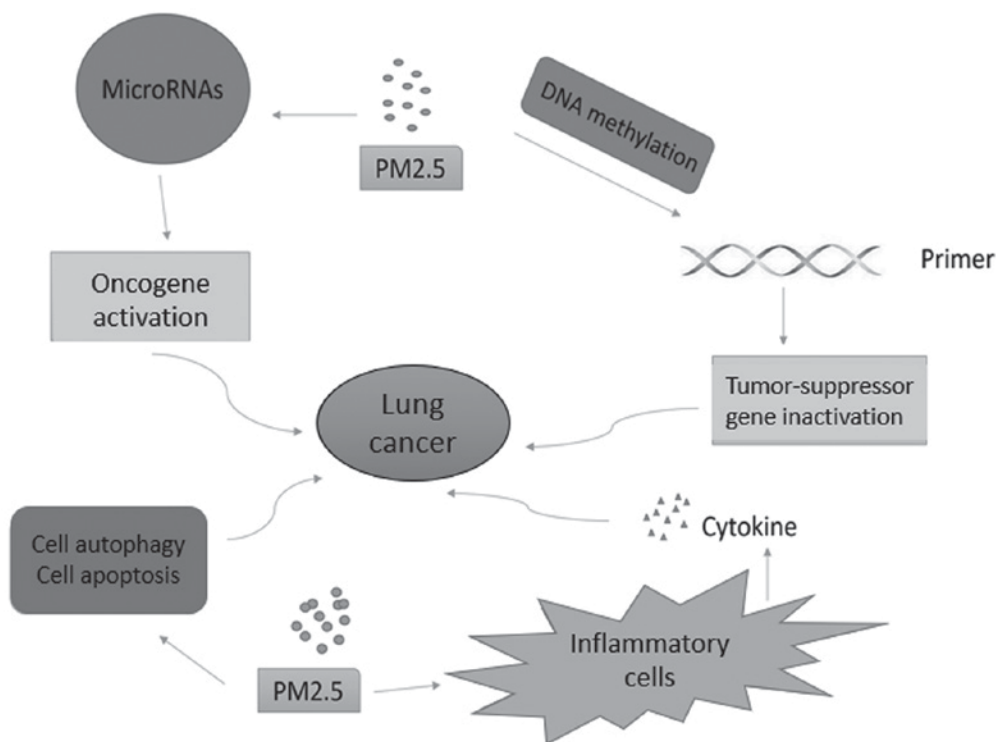
Figure 1. Function of PM2.5 in the pathogenesis of lung cancer. PM2.5 induces oncogene activation and tumor suppressor gene inactivation through microRNA dysregulation and DNA methylation in lung cancer. Tumor microenvironment alteration is also detected in PM2.5-induced inflammatory cells. PM2.5, particulate matter 2.5.
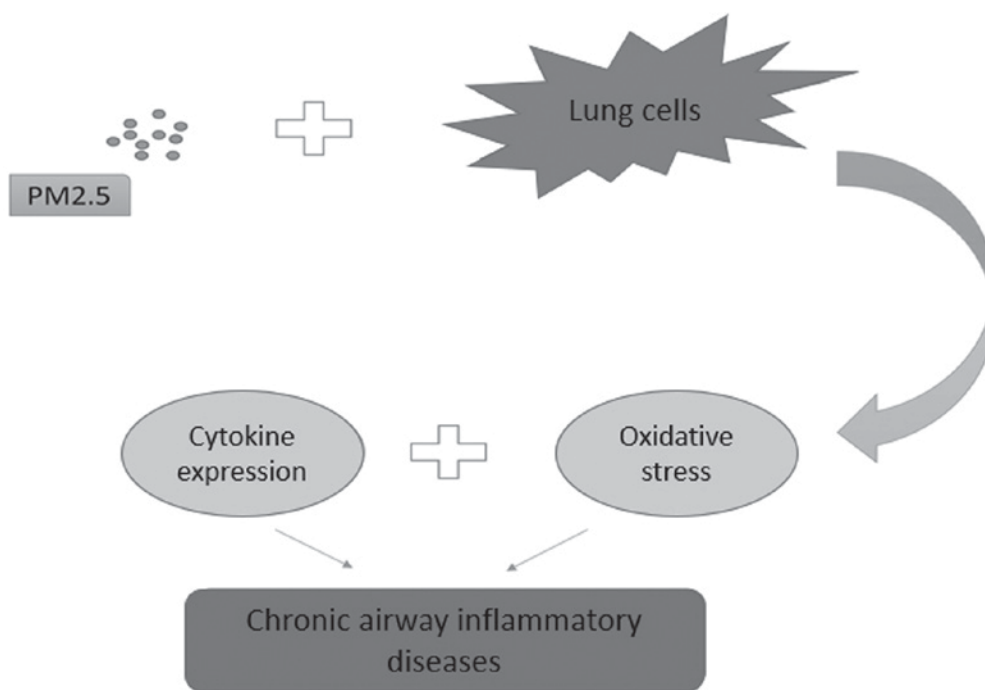

Figure 2. Function of PM2.5 in the pathogenesis of chronic airway inflammatory diseases. PM2.5 affects normal lung cells in chronic airway inflammatory diseases by affecting cytokine expression and oxidative stress. PM2.5, particulate matter 2.5.

COPD is a type of obstructive lung disease characterized by long-term poor airflow, which typically worsens over time (86). Numerous studies have demonstrated that AECOPD is associated with air pollution, particularly PM2.5 (87). Each additional 10 μg/m^3 PM2.5 exposure has been demonstrated to increase the rate of coughing symptoms by 33% and expectoration symptoms by 23%, and to decrease the diurnal variation rate of peak expiratory flow in patients with COPD (88). Long-term exposure to PM2.5 has been demonstrated to decrease the population forced expiratory volume in 1 sec

and the forced vital capacity, accelerating the decline in lung function in healthy adults in a population-based cohort (89). Therefore, preventive medication is required to avoid exacerbation of COPD following exposure to PM2.5 (90).

PM2.5-induced inflammatory response and oxidative stress. Oxidative stress is able to modulate critical signal transduction pathways, including NF-κB signaling, and histone modifications; alterations which are crucial in lung inflammation (91). PM2.5 has been demonstrated to increase the expression of inflammatory cytokine receptors, which are able to activate IL-1 receptor (IL-1R)- and IL-6R-mediated signaling pathways in cells of the lung (92). In a previous study, short-term exposure of PM2.5 to mice induced inflammatory cell infiltration and lung tissue congestion, increasing the expression of inflammatory mediators, including TNF-α, IL-6 and IL-1β, and oncogenes, including c-Fos and c-Jun, which dysregulated a variety of metabolic enzyme activities, including superoxide dismutase and nitric oxide synthase (93). It has been reported that lung oxidative stress and inflammation may be induced by a low dose of PM2.5 in healthy mice (94).

PM2.5 has been demonstrated to increase the level of NF-E2-related factor 2 (Nrf2) expression in mice with COPD, and Nrf2 was associated with oxidative stress (95). PM2.5 exposure was observed to increase the expression of IL-8 *in vitro*, which was mediated by oxidative stress and endocytosis (96). The enhanced expression of TNF-α and IL-6 has also been detected in sub-chronic (PM2.5 tracheal instillation once a week for 1, 3 or 6 months) PM2.5-exposed mice with COPD, and it is known that cytokine overexpression is able to aggravate immune system damage (97).

Sub-chronic exposure to PM2.5 has also been indicated to induce inflammatory injury in rats and impair the phagocytic function of AM (alveolar macrophage) (98). Furthermore, PM2.5 has been demonstrated to increase the phagocytic ability of macrophages in mice with COPD, thus increasing oxidative stress (99). PM2.5 also impairs the immune balance of mice with COPD by blocking the Notch signaling pathway (99). Exposing nasal mucosa epithelial cells to PM2.5 indicated that PM2.5 was able to increase ROS and Nrf2 levels, which have an association with oxidative stress (100). This study also revealed that PM2.5 increased the release of GM-CSF, TNF-α and IL-13, accelerating the inflammatory reaction. Previous research has revealed that the process of inflammation and oxidative stress occur via different pathways (101), and different PM sources may result in different ROS viabilities (102). In order to explore the function of PM2.5 in the pathogenesis of asthma, one research group exposed asthmatic mice to PM2.5, revealing that the content of IL-4 and IL-10, mediated by TNF-α and T helper 2 cells, increased, coupled with the decreased content of INF-γ mediated by T helper 1 cells. Inflammatory infiltration and goblet cell metaplasia were also demonstrated to be accelerated following PM2.5 exposure (103). The acute inflammatory response following PM2.5 exposure has been revealed to involve TLR2 and TLR4, and a T helper 2 cell-mediated immune response was also detected (104). Furthermore, PM was demonstrated to induce T helper 1/2 cell inflammatory

responses in healthy mice and may contribute to the initial onset of asthma (105).

5. PM2.5-induced pathogenesis in lung tuberculosis

Tuberculosis is a common chronic infectious disease caused by *Mycobacterium tuberculosis*, which is able to invade multiple organs, including the lungs (106). However, few studies have investigated the association between PM2.5 and pulmonary tuberculosis. It has been demonstrated that PM2.5 exposure in factory environments and smear-positive tuberculosis are associated; however, PM2.5 exposure in highway environments and smear-positive tuberculosis were not associated (107). PM2.5 exposure has been suggested to decrease the expression of hemoglobin subunit d2 and 3 in type II alveolar epithelial cells, increasing the risk of *M. tuberculosis* proliferation (108).

6. PM2.5-induced pathogenesis in respiratory infection

Respiratory infection may be characterized into upper and lower respiratory tract infections (109). It has been revealed that air pollution PM may alter anti-mycobacterial respiratory epithelium innate immunity systems (110). A European cohort study demonstrated that early childhood pneumonia was associated with air pollutants (111). Another study suggested that organic compounds in PM2.5 are able to aggravate the infection of upper and lower respiratory tract infections in children (112). It has also been indicated that the DNA repair gene xeroderma pigmentosum complementation group C may serve an essential function in the pathogenesis of PM2.5-induced bronchitis (113). To the best of our knowledge, the effect of PM2.5 in respiratory infection has not been demonstrated.

7. Conclusions

From the present review, the following conclusions can be inferred. The chemical properties and pathological toxicity of PM2.5 are known to influence a variety of respiratory diseases. Previous research has focused on the epidemiology and toxicology of PM2.5; however, more recent research has investigated the function that PM2.5 serves in the pathogenesis of respiratory diseases. PM2.5-induced epigenetic changes, including microRNA dysregulation (37) and DNA methylation (46), microenvironment alteration (53), cell autophagy and apoptosis (67,68), may result in oncogene activation and tumor suppressor gene inactivation in lung cancer (Fig. 1). By activating inflammatory-associated cells (93), including T helper 2 cells, and triggering oxidative stress (97), PM2.5 may induce and aggravate asthma and COPD (Fig. 2). PM2.5-induced alteration of molecular mechanisms in pulmonary tuberculosis and respiratory infection remain unclear. Furthermore, the properties of PM2.5 often vary with environmental changes, and further clarification is required.

Investigating the impact of PM2.5 on respiratory disease is essential, since numerous populations are currently experiencing heavy pollution. Understanding the molecular mechanisms of PM2.5-induced respiratory diseases may

contribute to the development of targeted drugs and preventive treatments.

Availability of data and materials

Not applicable.

Authors' contributions

RL was responsible for the acquisition, analysis and summarizing of data, drafting the manuscript and revising it. RZ was involved in analyzing and interpreting the manuscript, and giving final approval of the version to be published. JZ has made substantial contributions to the conception and design of the present study. RZ and JZ are accountable for all aspects of the work.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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