Review Article

The Correlation of PM2.5 Exposure with Acute Attack and Steroid Sensitivity in Asthma

Jingjing Luo, Han Liu, Shucheng Hua, and Lei Song

Department of Respiratory Medicine, Center for Pathogen Biology and Infectious Diseases, Key Laboratory of Organ Regeneration and Transplantation of the Ministry of Education, The First Hospital of Jilin University, Changchun 130021, China

Correspondence should be addressed to Shucheng Hua; hsc@jlu.edu.cn and Lei Song; lsong@jlu.edu.cn

Received 30 June 2022; Revised 5 August 2022; Accepted 8 August 2022; Published 18 August 2022

Academic Editor: Jianfeng Wang

Copyright © 2022 Jingjing Luo et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Bronchial asthma is one of the most common chronic inflammatory diseases of the respiratory system. Asthma primarily manifests in reversible airflow limitation and airway inflammation, airway remodeling, and persistent airway hyperresponsiveness. PM2.5, also known as fine particulate matter, is the main component of air pollution and refers to particulate matter with an aerodynamic diameter of ≤2.5 μm. PM2.5 can be suspended in the air for an extensive time and, in addition, can contain or adsorb heavy metals, toxic gases, polycyclic aromatic hydrocarbons, bacterial viruses, and other harmful substances. Epidemiological studies have demonstrated that, in addition to increasing the incidence of asthma, PM2.5 exposure results in a significant increase in the incidence of hospital visits and deaths due to acute asthma attacks. Furthermore, PM2.5 was reported to induce glucocorticoid resistance in asthmatic individuals. Although various countries have implemented strict control measures, due to the wide range of PM2.5 sources, complex components, and unknown pathogenic mechanisms involving the atmosphere, environment, chemistry, and toxicology, PM2.5 damage to human health still cannot be effectively controlled. In this present review, we summarized the current knowledge base regarding the relationship between PM2.5 toxicity and the onset, acute attack prevalence, and steroid sensitivity in asthma.

1. Introduction

With increasing levels of smog in cities worldwide, the impact of air pollution on human health is attracting global attention. PM2.5, also known as fine particulate matter, is the main component of air pollution and refers to particulate matter with an aerodynamic diameter of ≤2.5 μm in the atmosphere [1]. PM2.5 can be suspended in the air for an extensive time and, in addition, can contain or adsorb heavy metals, toxic gases, polycyclic aromatic hydrocarbons, bacterial viruses, and other harmful substances. Moreover, PM2.5 can enter the bronchi and alveoli before finally entering the blood, causing damage to multiple organs, especially those of the respiratory and cardiovascular systems [2–5]. The Global Environment Outlook 5 released by the United Nations Environment Program in 2012 highlighted that the fine particles in air pollution cause more than two million deaths globally every year and cause huge economic losses. With the rapid development of economy and industry, China has become substantially affected by PM2.5 ambient air pollution. According to a study conducted in 2010 by the School of Public Health of Peking University, in only 4 cities (Beijing, Shanghai, Guangzhou, and Xi’an), 7,770 premature deaths were reported to be caused by PM2.5 pollution, associated with an economic loss of 6.17 billion Yuan [6]. Although various countries have implemented strict control measures, due to the wide range of PM2.5 sources, complex components, and unknown pathogenic mechanisms involving the atmosphere, environment, chemistry, and toxicology, PM2.5 damage to human health still cannot be effectively controlled. Therefore, it is of great practical significance to prevent and control PM2.5 exposure.

Bronchial asthma is one of the most common chronic lung diseases. It is currently estimated that around 5%-16% of the global population suffers from asthma, and about 250,000 people die from asthma attacks every year. With gradual atmospheric deterioration due to pollution, the
morbidity and mortality rates of asthma are increasing [7]. Epidemiological studies have demonstrated that PM2.5 levels in the atmosphere are positively correlated with the incidence of asthma, the number of hospitalizations, and the number of emergency room admissions, prolonging the number of days patients spend in hospital and increasing hospitalization costs [8–10]. Glucocorticoids (GCs) are the first-line treatment for asthma; they have been shown to significantly reduce inflammation of the respiratory tract and ameliorate impaired lung function. Most patients have satisfactory treatment outcomes with GCs alone, or in combination with β-receptor agonists. However, clinical and scientific studies have demonstrated that exposure to pollutants such as fine particulate matter, ozone, and cigarettes can reduce the sensitivity of asthma patients to GCs and increase the amount of GCs required for asthma symptom control, resulting in increased occurrences of drug side effects and difficulties in the clinical treatment of asthma [11–13].

2. PM2.5 Exposure and Incidence of Asthma

PM2.5 exposure results in a chronic nonspecific inflammatory disease of the airway mediated by a variety of inflammatory cells dominated by mast cells, eosinophils, and T cells and their secreted cytokines, primarily manifesting as reversible airflow limitation, airway inflammation, airway remodeling, and hyperresponsiveness [14]. Studies have reported that inhalable particulate matter such as PM2.5 is capable of carrying a substantial quantity of allergens such as microorganisms, organic compounds, and metals, which have been shown to induce type I hypersensitivity and increase the risk of asthma [15]. A study by Carlsten et al. revealed that an interquartile range (IQR) of PM2.5 concentration at birth year of 4.1 μg/m³ significantly increased the risk of developing asthma in children (OR, 3.1; 95% CI: 1.3-7.4) [16]. Moreover, PM2.5 exposure increases the risk of asthma in adults, and further, exposure of pregnant women to high levels of PM2.5 during pregnancy increases the risk of asthma in newborns [17, 18]. Conversely, the biological activity of PM2.5 has been demonstrated to aggravate pathological processes such as airway hyperresponsiveness and remodeling by promoting airway inflammation and oxidative stress. Overall, it is clear that when the atmospheric level of ambient PM2.5 rises sharply, the number of outpatients and hospitalizations for respiratory diseases such as asthma increases significantly [17].

2.1. PM2.5 Exposure Induces Acute Asthma Attacks. Acute asthma attack refers to the exacerbation of airway inflammation and airflow limitation in patients, during infection or on inhalation of allergens or air pollution. Acute asthma attack usually requires systemic glucocorticoid therapy [19]. Although most acute attacks are relieved by bronchodilator combined with hormone therapy, repeated asthma attacks can lead to aggravated and irreversible pathological pulmonary changes such as airway remodeling [20]. The most common cause of acute asthma attack is respiratory infection, but accompanied by the gradual deterioration of human living environments, air pollution has become another risk factor for acute asthma attack that cannot be ignored.

Inhalable particulate matter such as PM2.5 carries a large number of allergens that can induce type I hypersensitivity reactions; these include microorganisms, organic compounds, and metals. Organic matter (OM), black carbon (BC), and SO42– were demonstrated to contribute more to the risk of asthma in early life when compared to other PM2.5 constituents. Among them, the effects of BC were only identified during pregnancy. Early-life exposures to ambient PM2.5, particularly OM, BC, and SO42–, are associated with an increased risk of childhood asthma [21]. In addition to being associated with asthma, PM2.5 exposure is an independent risk factor for acute asthma attacks. Epidemiological studies have revealed that elevation in ambient PM2.5 levels by 10 μg/m³ resulted in increased risk of respiratory symptoms (cough, wheezing, or dyspnea) in asthmatic children by 21% and an increase in the rate of visits for asthma attacks in adults by 13.75% [22]. The potential for PM2.5 to induce asthma attacks is greater than that of PM10 and ozone [22], and its effect during warm seasons (20.09% increase in asthma visitation rate) is significantly higher than during cold seasons (2.39%) [23]. Since children have reduced airway defense mechanisms and a higher level of inhaled gas per kilogram of body weight than adults, the effect of elevated ambient PM2.5 concentrations on childhood asthma attacks appears to be more pronounced, with a higher rate of exacerbations reported in male children than in female children [17, 24–26]. Studies by Hua et al. [27] and Xie et al. [28] demonstrated that elevated PM2.5 concentrations are also closely related to acute asthma attacks in the Chinese population.

Evidence generated by basic research further supports the epidemiological view that PM2.5 exposure induces asthma attacks, in addition to causing phenotypic changes in alveolar macrophage populations (upregulation of CD14, CD11b, and HLA-DR expression) and their increased synthesis [29]. Moreover, PM2.5 has been reported to stimulate the synthesis and release of macrophage and epithelial cells in the lung. Interleukin- (IL-) 6 and IL-8 exert chemoattractive effects upon neutrophils [30, 31]. Intraperitoneal injection or intranasal instillation of PM2.5 was reported to induce eosinophilic infiltration in the airways, elevated Th2 cytokines in bronchoalveolar lavage fluid, and airway hyperresponsiveness in mice with allergic asthma phenotypes [32, 33]. Furthermore, He et al. identified that airway instillation of PM2.5 induced neutrophilic alveolar and bronchitis in mice, while combined ovalbumin (OVA) and PM2.5 airway instillation resulted in massive lung eosinophilic granulocyte infiltration and increased expression of Th2 cytokines, such as IL-13 and IL-4, which caused mice to develop symptoms similar to acute asthma attack [34]. In asthma models that have been sensitized by OVA, PM2.5 exposure induced inflammatory cell infiltration and increased the levels of inflammatory factors, goblet cell metaplasia, and changes in lung ultrastructure [35, 36].

2.2. The Role of Oxidative Stress in PM2.5-Induced Asthma Attack. During normal physiological processes, reactive
2.3. PM2.5 and MicroRNA. MicroRNAs (miRNAs, miRNAs) are a class of endogenous, 18-25 nt, noncoding small RNA molecules that are widespread and highly conserved in eukaryotic cells. miRNA does not have an open reading frame; it induces degradation of target mRNA or inhibits its transcription by binding to the 3’ untranslated region (3’ UTR), playing an important role in gene regulation [48]. miRNAs regulate about 1/3 of human gene expression and have been implicated in pathological and physiological processes such as inflammation, oxidative stress, stem cell development, tumor growth, and metastasis [49–51]. Recently, studies have further confirmed that microRNAs play an important regulatory role in PM2.5-mediated toxicity (Figure 1). For example, PM2.5 exposure caused downregulation of 138 miRNAs, including miR-182 and miR-185, in mouse embryonic NIH3T3 cells. Moreover, PM2.5 resulted in downregulation of miR-182 and miR-185, leading to upregulated expression of targets SLC30A1, SERPINB2, and AKR1C1 and eventually inducing NIH3T3 cell malignant fibrosarcoma in nude mice [52]. Using bronchial brushing, Rider et al. obtained airway epithelial cells from 13 volunteers before and after PM2.5 exposure and compared the changes in their cellular transcriptome. The results revealed that the expression of various miRNAs and mRNAs involved in immune and inflammatory responses was significantly altered [53]. Let-7a was downregulated in airway epithelial cells in response to PM2.5 exposure, leading to an increase in the expression of Arginase 2, which aggravated oxidative stress-induced cellular injury [54]. Furthermore, Song et al. reported that PM2.5 exposure downregulated miR-331 expression in the human airway epithelial cell line Beas 2B, resulting in increased expression of NF-κB and aberrant activation of NF-κB [55]. In addition, some studies have demonstrated that abnormal expression of miRNA is involved in the process wherein PM2.5 promotes the occurrence and development of lung cancer [56–58].

3. PM2.5 Exposure and Asthma Treatment

In addition to being attributable to the occurrence and development of asthma, inhalable particulate matter such as PM2.5 further impacts the treatment of asthma. Both Slaughter et al. [12] and Gent et al. [59] identified that PM2.5 not only increased the risk of asthma but also increased the use of inhaled drugs to rescue illness. von Klot et al. [60] reported that the concentration of inhalable particulate matter of various diameters, including PM2.5, was related to the amount of inhaled GCs used by asthma patients; this was the case whether it was the PM2.5 concentration on the day or the average PM2.5 on the 5th or 14th day. High PM2.5 concentrations were further shown to significantly increase the level of GCs required. Another study revealed that PM2.5 concentration was related to the amount of oral GCs required by asthmatic patients, especially adult patients [61]. Furthermore, some studies have demonstrated that smoking, as an important source of PM2.5, can reduce the activity of histone deacetylase 2 (HDAC2) and mediate hormone resistance, which is an important factor affecting the sensitivity to GCs in respiratory diseases such as asthma and COPD. However, there is...
no direct clinical and basic research evidence to confirm the effect and mechanism of PM2.5 on the sensitivity of asthmatic GCs. Therefore, there is an urgent requirement to further combine clinical and basic medicine to further verify and interpret the effect and mechanism of PM2.5 on GC sensitivity in animal models and at cellular and molecular levels. Studies of this kind may provide theoretical references for the treatment and intervention of asthma patients under environmental deterioration.

Although PM2.5 is associated with a variety of diseases, the pathological mechanism by which PM2.5 causes tissue damage has not been fully described. Existing evidence demonstrates that the main components of PM2.5, carbon particles, metal ions, and organic aromatic hydrocarbons, not only cause oxidative damage to cell membranes and DNA but also trigger downstream signaling pathways. Such pathways include NF-κB, mitogen-activated protein kinase (MAPK), and PI3K [62–64], which act to potentiate inflammation and apoptosis in tissues.

In recent years, studies have confirmed that the three main subfamilies of the MAPK family, ERK, c-Jun N-terminal kinase (JNK), and p38 MAPK, are involved in PM2.5-mediated inflammatory response and cell damage (Figure 2). For example, in lung epithelial cells, RNA-sequencing identified that MAPK pathway-related genes are activated and are closely related to inflammatory damage in cells. It was reported that PM2.5 exposure increased the levels of phosphorylation of ERK, JNK, and p38 MAPK in cardiomyocyte H9c2 cells, and p38 MAPK promoted inflammation. Meanwhile, ERK protected cells from PM2.5-induced apoptosis. Corsini et al. reported that PM2.5 induced the release of inflammatory factor IL-8 from lung epithelial cells (A549) and macrophage (THP-1). Conversely, inhibition of p38 MAPK attenuated PM2.5-mediated IL-8 release, suggesting that p38 MAPK is an important pathway that mediates inflammatory response to PM2.5. In addition, activation of the MAPK pathway in the myocardium and airway epithelium was observed in mouse and rat models of PM2.5 exposure.

As a steroid hormone, GCs bind to the receptor GRα on the target cell membrane (GC receptors are divided into GRα and GRβ, and GRβ does not regulate gene transcription). GRα is activated, and transfer into the nucleus causes it to bind to DNA. Glucocorticoid response elements (GRE) bind to other transcription factors to form a transcription initiation complex that regulates the expression of downstream target genes [65]. Any abnormality in this link can cause asthma GC resistance. A small number of asthmatic patients are resistant to GC treatment due to the reduced availability of GCs caused by genetic susceptibility [66] or the reduced capacity of GRα in binding GCs [67]. The responses of asthma patients to GC therapy are extremely complex due to the joint participation of acquired factors such as environment, infection, and the multiple signaling pathways mediated by a plethora of cytokines. Among them, MAPK activation-mediated GRα intranuclear transport disorder plays an extremely important role in the resistance of asthmatics to GC treatment.

MAPK can regulate the binding ability and stability of GRα and GCs and the ability of GRα to transfer into the nucleus to form a transcription complex, by specifically phosphorylating some serine residues in GRα. For example, phosphorylation of Ser226 of GRα by JNK leads to enhanced GRα translocation out of the nucleus [68]. Meanwhile, phosphorylation of Ser211 by p38 MAPK inhibits the translocation of GRα into the nucleus [69], causing GC resistance. In peripheral blood monocytes (PBMC) of GC-resistant patients, the abnormal activation of the p38 MAPK signaling pathway is associated with the decreased efficacy of dexamethasone in inhibiting cytokine release. However, administration of the p38 MAPK inhibitor can restore the effect of dexamethasone on lipopolysaccharide-induced inhibition of IL-8 release [70]. Chang et al. [71, 72] demonstrated the occurrence of excessive activation of p38 MAPK in the lung smooth muscle cells of patients with severe asthma, and the inhibition of p38 MAPK enhanced the efficacy of GCs in reducing tumor necrosis factor alpha- (TNF-α-) mediated inflammatory response. In addition, the activation of JNK was also significantly increased in the PBMC and bronchial biopsy tissues of GC-resistant patients, and administration of high-dose oral corticosteroids did not reduce its activation level [73].
Although PM2.5 has been confirmed to be associated with MAPK activation, due to research on the pathogenesis of PM2.5 being in its early stages, there are relatively few related reports. It will be of clinical importance to determine the role that MAPK plays in PM2.5-related diseases. In particular, the regulatory mechanism of PM2.5-mediated MAPK activation remains to be revealed by further research.

4. Perspective

The studies described herein suggest that PM2.5 exposure aggravates the progression of asthma by mediating oxidative stress. However, the specific regulatory mechanisms and networks by which PM2.5 mediates oxidative stress are not yet fully understood. Research on the effects of the mechanism of PM2.5 toxicity will pave the way for development of targeted drugs. Importantly, therapeutic approaches derived from natural chemicals and novel drug delivery systems shed light on the prevention of PM2.5 toxicity in the respiratory system [74–76]. Coordinating disparate disciplines within the study of PM2.5 toxicity mechanisms will provide comprehensive cross-over advantages and has important practical significance for the formulation of prevention and control intervention strategies for the asthmatic population exposed to PM2.5.

Data Availability

The data used to support the findings of this study are included within the article.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors’ Contributions

Jingjing Luo and Han Liu contributed equally.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (grant U20A20342) and Jilin Provincial Development and Reform Commission (2016C043-1).

References

[1] P. Thangavel, D. Park, and Y. C. Lee, “Recent insights into particulate matter (PM2.5)-mediated toxicity in humans: an overview,” International Journal of Environmental Research and Public Health, vol. 19, p. 7511, 2022.
[2] N. Pritchett, E. C. Spangler, G. M. Gray et al., “Exposure to outdoor particulate matter air pollution and risk of gastrointestinal cancers in adults: a systematic review and meta-analysis of epidemiologic evidence,” Environmental Health Perspectives, vol. 130, no. 3, p. 36001, 2022.
[3] L. Rasking, K. Vanbrabant, H. Bové et al., “Adverse effects of fine particulate matter on human kidney functioning: a systematic review,” Environmental Health, vol. 21, no. 1, p. 24, 2022.
[4] T. Zhao, W. Qi, P. Yang et al., “Mechanisms of cardiovascular toxicity induced by PM2.5: a review,” Environmental Science
A. Fuhlbrigge, D. Peden, A. J. Apter et al., “Airway hyperresponsiveness development and the toxicity of PM2.5,” *Environmental Science and Pollution Research International*, vol. 28, no. 6, pp. 6374–6391, 2021.

G. Li and X. C. Pan, “Evaluation of excess mortality caused by PM2.5 in four typical Chinese big cities,” *Zhonghua Yi Xue Za Zhi*, vol. 93, pp. 2703–2706, 2013.

F. D. Martinez and D. Vercelli, “Asthma,” *Lancet*, vol. 382, pp. 1360–1372, 2013.

K. Berhane, C. C. Chang, R. McConnell et al., “Association of changes in air quality with bronchitic symptoms in children in California, 1993–2012,” *JAMA*, vol. 315, no. 14, pp. 1491–1501, 2016.

T. Teresa, J. Zhu, K. Larsen et al., “Progression from asthma to chronic obstructive pulmonary disease: Is air pollution a risk factor?,” *American Journal of Respiratory and Critical Care Medicine*, vol. 194, no. 4, pp. 429–438, 2016.

R. W. Atkinson, S. Kang, H. R. Anderson, J. C. Mills, and H. A. Walton, “Epidemiological time series studies of PM2.5 and daily mortality and hospital admissions: a systematic review and meta-analysis,” *Thorax*, vol. 69, no. 7, pp. 660–665, 2014.

R. T. Cohen, B. A. Raby, K. van Steen et al., “In utero smoke exposure and impaired response to inhaled corticosteroids in children with asthma,” *The Journal of Allergy and Clinical Immunology*, vol. 126, pp. 491–497, 2010.

J. C. Slaughter, T. Lummley, L. Sheppard, J. Q. Koenig, and G. G. Shapiro, “Effects of ambient air pollution on symptom severity and medication use in children with asthma,” *Annals of Allergy, Asthma & Immunology: Official Publication of the American College of Allergy, Asthma, & Immunology*, vol. 91, no. 4, pp. 346–353, 2003.

A. Bao, F. Li, M. Zhang, Y. Chen, P. Zhang, and X. Zhou, “Impact of ozone exposure on the response to glucocorticoid in a mouse model of asthma: involvements of p38 MAPK and MKP-1,” *Respiratory Research*, vol. 15, no. 1, p. 126, 2014.

M. Lommatsch, “Immune modulation in asthma: current concepts and future strategies,” *Respiration*, vol. 99, no. 7, pp. 566–576, 2020.

K. Liu, S. Hua, and L. Song, “PM2.5 exposure and asthma development: the key role of oxidative stress,” *Oxidative Medicine and Cellular Longevity*, vol. 2022, Article ID 3618806, 12 pages, 2022.

C. Carlsten, A. Dybuncio, A. Becker, M. Chan-Yeung, and M. Brauer, “Traffic-related air pollution and incident asthma in a high-risk birth cohort,” *Occupational and Environmental Medicine*, vol. 68, no. 4, pp. 291–295, 2011.

X. Y. Zheng, H. Ding, L. N. Jiang et al., “Association between air pollutants and asthma emergency room visits and hospital admissions in time series studies: a systematic review and meta-analysis,” *PloS One*, vol. 10, no. 9, article e0138146, 2015.

H. H. Leon Hsu, Y. H. Mathilda Chiu, B. A. Coull et al., “Pre-natal particulate air pollution and asthma onset in urban children,” *Identifying Sensitive Windows and Sex Differences. American Journal of Respiratory and Critical Care Medicine*, vol. 192, pp. 1052–1059, 2015.

A. Fuhlbrigge, D. Peden, A. J. Apter et al., “Asthma outcomes: exacerbations,” *The Journal of Allergy and Clinical Immunology*, vol. 129, no. 3, pp. S34–S48, 2012.

D. J. Jackson, A. Sykes, P. Mallia, and S. L. Johnston, “Asthma exacerbations: origin, effect, and prevention,” *The Journal of Allergy and Clinical Immunology*, vol. 128, no. 6, pp. 1165–1174, 2011.

Y. Zhang, Z. Yin, P. Zhou et al., “Early-life exposure to PM_{2.5} constituents and childhood asthma and wheezing: findings from China, Children, Homes, Health study,” *Environment International*, vol. 165, article 107297, 2022.

L. Romieu, F. Meneses, S. Ruiz et al., “Effects of air pollution on the respiratory health of asthmatic children living in Mexico City,” *American Journal of Respiratory and Critical Care Medicine*, vol. 154, no. 2, pp. 300–307, 1996.

S. Rodopoulou, E. Samoli, M. C. Chalbot, and I. G. Kavouras, “Air pollution and cardiovascular and respiratory emergency visits in Central Arkansas: a time-series analysis,” *The Science of the Total Environment*, vol. 536, pp. 872–879, 2015.

L. F. Tétrelault, M. Doucet, P. Gamache et al., “Severe and moderate asthma exacerbations in asthmatic children and exposure to ambient air pollutants,” *International Journal of Environmental Research and Public Health*, vol. 13, no. 8, p. 771, 2016.

H. Lim, H. J. Kwon, J. A. Lim et al., “Short-term effect of fine particulate matter on children’s hospital admissions and emergency department visits for asthma: a systematic review and meta-analysis,” *Journal of Preventive Medicine and Public Health*, vol. 49, pp. 205–219, 2016.

K. A. Evans, J. S. Halterman, P. K. Hopke, M. Fagnano, and D. Q. Rich, “Increased ultrafine particles and carbon monoxide concentrations are associated with asthma exacerbation among urban children,” *Environmental Research*, vol. 129, pp. 11–19, 2014.

J. Hua, Y. Yin, L. Peng, L. du, F. Geng, and L. Zhu, “Acute effects of black carbon and PM_{2.5} on children asthma admissions: a time-series study in a Chinese city,” *The Science of the Total Environment*, vol. 481, pp. 433–438, 2014.

Y. B. Xie, J. Chen, and W. Li, “An assessment of PM2.5 related health risks and impaired values of Beijing residents in a consecutive high-level exposure during heavy haze days,” *Huan Jing ke Xue= Huanjing Kexue*, vol. 35, pp. 1–8, 2014.

N. E. Alexis, J. C. Lay, K. Zeman et al., “Biological material on inhaled coarse fraction particulate matter activates airway phagocytes _in vivo_ in healthy volunteers,” *The Journal of Allergy and Clinical Immunology*, vol. 117, no. 6, pp. 1396–1403, 2006.

Z. Zhou, Y. Liu, F. Duan et al., “Transcriptomic analyses of the biological effects of airborne PM2.5 exposure on human bronchial epithelial cells,” *PloS One*, vol. 10, article e0138267, 2015.

J. Shoenfeld, R. J. Mitkus, R. Zeisler et al., “Involvement of TLR2 and TLR4 in inflammatory immune responses induced by fine and coarse ambient air particulate matter,” *Journal of Leukocyte Biology*, vol. 86, no. 2, pp. 303–312, 2009.

K. Ogino, R. Zhang, H. Takahashi et al., “Allergic airway inflammation by nasal inoculation of particulate matter (PM2.5) in NC/Nga mice,” *PloS One*, vol. 9, article e92710, 2014.

K. Ogino, K. Nagaoka, T. Okuda et al., “PM2.5-induced airway inflammation and hyperresponsiveness in NC/Nga mice,” *Environmental Toxicology*, vol. 32, no. 3, pp. 1047–1054, 2017.

M. He, T. Ichinose, Y. Ren et al., “PM2.5-rich dust collected from the air in Fukuoka, Kyushu, Japan, can exacerbate murine lung eosinophilia,” *Inhalation Toxicology*, vol. 27, no. 6, pp. 287–299, 2015.
[35] J. R. Harkema, G. Keeler, J. Wagner et al., “Effects of concentrated ambient particles on normal and hypersecretory airways in rats,” Research, vol. 120, pp. 69–79, 2004.

[36] X. Zhang, W. Zhong, Q. Meng et al., “Ambient PM2.5 exposure exacerbates severity of allergic asthma in previously sensitized mice,” The Journal of Asthma : Official Journal of the Association for the Care of Asthma, vol. 52, no. 8, pp. 785–794, 2015.

[37] G. Pizzino, N. Irrera, M. Cucinotta et al., “Oxidative stress: harms and benefits for human health,” Oxidative Medicine and Cellular Longevity, vol. 2017, Article ID 8416763, 13 pages, 2017.

[38] A. Nunomura, R. J. Castellani, X. Zhu, P. I. Moreira, G. Perry, and M. A. Smith, “Involvement of oxidative stress in Alzheimer disease,” Journal of Neuropathology and Experimental Neurology, vol. 65, no. 7, pp. 631–641, 2006.

[39] H. J. Forman and H. Zhang, “Targeting oxidative stress in disease: promise and limitations of antioxidant therapy,” Nature Reviews. Drug Discovery, vol. 20, no. 9, pp. 689–709, 2021.

[40] A. Bacci, L. Pan, X. Ba, and I. Boldogh, “Pathophysiology of bronchoconstriction: role of oxidatively damaged DNA repair,” Current Opinion in Allergy and Clinical Immunology, vol. 16, no. 1, pp. 59–67, 2016.

[41] L. He, C. Norris, X. Cui et al., “Personal exposure to PM2.5 oxidative potential in association with pulmonary pathophysiologic outcomes in children with asthma,” Environmental Science & Technology, vol. 55, no. 5, pp. 3101–3111, 2021.

[42] M. P. Sierra-Vargas, A. M. Guzman-Grenfell, S. Blanco-Jimenez et al., “Airborne particulate matter PM2.5 from Mexico City affects the generation of reactive oxygen species by blood neutrophils from asthmatics: an in vitro approach,” Journal of Occupational Medicine and Toxicology, vol. 4, p. 17, 2009.

[43] M. J. Rosa, B. Yan, S. N. Chillrud et al., “Domestic airborne black carbon levels and 8-iso prostane in exhaled breath condensate among children in New York City,” Environmental Research, vol. 135, pp. 105–110, 2014.

[44] S. Hussain, R. Laumbach, J. Coleman et al., “Controlled exposure to diesel exhaust causes increased nitrite in exhaled breath condensate among subjects with asthma,” Journal of Occupational and Environmental Medicine, vol. 54, no. 10, pp. 1186–1191, 2012.

[45] S. A. Weichenthal, E. Lavigne, G. J. Evans, K. J. Godri Pollitt, and R. T. Burnett, “Fine particulate matter and emergency room visits for respiratory Illness. Effect modification by oxidative potential,” American Journal of Respiratory and Critical Care Medicine, vol. 194, no. 5, pp. 577–586, 2016.

[46] A. Yang, N. A. Janssen, B. Brunekeef et al., “Children’s respiratory health and oxidative potential of PM2.5: the PIAMA birth cohort study,” Occupational and Environmental Medicine, vol. 73, no. 3, pp. 154–160, 2016.

[47] J. T. Bates, R. J. Weber, J. Abrams et al., “Reactive oxygen species generation linked to sources of atmospheric particulate matter and cardiopulmonary effects,” Environmental Science & Technology, vol. 49, no. 22, pp. 13605–13612, 2015.

[48] H. O. Iwakawa and Y. Tomari, “The functions of microRNAs: mRNA decay and translational repression,” Trends in Cell Biology, vol. 25, no. 11, pp. 651–665, 2015.

[49] S. Jonas and E. Izaurralde, “Towards a molecular understanding of microRNA-mediated gene silencing,” Nature Reviews. Genetics, vol. 16, no. 7, pp. 421–433, 2015.

[50] J. Gao, L. Song, H. Xia, L. Peng, and Z. Wen, “6-O-galloyl-panaxifolin regulates proliferation and metastasis of non-small cell lung cancer through AMPK/miR-299-5p/ATF2 axis,” Respiratory Research, vol. 21, no. 1, p. 39, 2020.

[51] L. Song, L. Peng, S. Hua et al., “miR-144-5p enhances the radiosensitivity of non-small-cell lung cancer cells via targeting ATF2,” BioMed Research International, vol. 2018, Article ID 5109497, 10 pages, 2018.

[52] C. Liu, H. Guo, X. Cheng et al., “Exposure to airborne PM2.5 suppresses microRNA expression and deregulates target oncogenes that cause neoplastic transformation in NIH3T3 cells,” Oncotarget, vol. 6, no. 30, pp. 29428–29439, 2015.

[53] C. F. Rider, M. Yamamoto, O. P. Günther et al., “Controlled diesel exhaust and allergen coexpression modulates microRNA and gene expression in humans: effects on inflammatory lung markers,” The Journal of Allergy and Clinical Immunology, vol. 138, no. 6, pp. 1690–1700, 2016.

[54] L. Song, D. Li, Y. Gu, X. Li, and L. Peng, “Let-7a inhibits particulate matter (<2.5 μum)-induced oxidative stress and injury in human airway epithelial cells by targeting arginase 2,” Journal of Applied Toxicology, vol. 36, pp. 1302–1310, 2016.

[55] L. Song, D. Li, X. Li et al., “Exposure to PM2.5 induces aberrant activation of NF-κB in human airway epithelial cells by down-regulating miR-331 expression,” Environmental Toxicology and Pharmacology, vol. 50, pp. 192–199, 2017.

[56] X. Li, Z. Ding, C. Zhang et al., “MicroRNA-122-3p inhibits apoptosis in A549 cells exposed to fine particulate matter,” Environmental Science and Pollution Research International, vol. 23, no. 10, pp. 10103–10113, 2016.

[57] X. Li, Y. Iw, N. Gao et al., “microRNA-802/Rnd3 pathway imposes on carcinogenesis and metastasis of fine particulate matter exposure,” Oncotarget, vol. 7, no. 23, pp. 35026–35043, 2016.

[58] J. Li, W. X. Li, C. Bai, and Y. Song, “Particulate matter-induced epigenetic changes and lung cancer,” The Clinical Respiratory Journal, vol. 11, no. 5, pp. 539–546, 2017.

[59] J. F. Gent, P. Koutrakis, K. Belanger et al., “Symptoms and medication use in children with asthma and traffic-related sources of fine particle pollution,” Environmental Health Perspectives, vol. 117, no. 7, pp. 1168–1174, 2009.

[60] S. von Klot, G. Wolke, T. Tuch et al., “Increased asthma medication use in association with ambient fine and ultrafine particles,” The European Respiratory Journal, vol. 20, no. 3, pp. 691–702, 2002.

[61] F. H. Johnston, R. J. Webby, L. S. Pilotto, R. S. Bailie, D. L. Parry, and S. J. Halpin, “Vegetation fires, particulate air pollution and asthma: a panel study in the Australian monsoon tropics,” International Journal of Environmental Health Research, vol. 16, no. 6, pp. 391–404, 2006.

[62] Z. Dagher, G. Garçon, S. Billet et al., “Role of nuclear factor-kappa B activation in the adverse effects induced by air pollution particulate matter (PM2.5) in human epithelial lung cells (L132) in culture,” Journal of Applied Toxicology : JAT, vol. 27, no. 3, pp. 284–290, 2007.

[63] J. Cao, G. Qin, R. Shi et al., “Overproduction of reactive oxygen species and activation of MAPKs are involved in apoptosis induced by PM in rat cardiac H9c2 cells,” Journal of Applied Toxicology : JAT, vol. 36, no. 4, pp. 609–617, 2016.

[64] X. Deng, W. Rui, F. Zhang, and W. Ding, “PM2.5 induces Nrf2-mediated defense mechanisms against oxidative stress...
by activating PIK3/AKT signaling pathway in human lung alveolar epithelial A549 cells,” *Cell Biology and Toxicology*, vol. 29, no. 3, pp. 143–157, 2013.

[65] M. Arango-Lievano, W. M. Lambert, and F. Jeanneteau, “Molecular biology of glucocorticoid signaling,” *Advances in Experimental Medicine and Biology*, vol. 872, pp. 33–57, 2015.

[66] S. Schmidt, J. Rainer, C. Ploner, E. Presul, S. Riml, and R. Kofler, “Glucocorticoid-induced apoptosis and glucocorticoid resistance: molecular mechanisms and clinical relevance,” *Cell Death and Differentiation*, vol. 11, Supplement 1, pp. S45–S55, 2004.

[67] E. Charmandari, T. Kino, E. Souvatzoglou, A. Vottero, N. Bhattacharyya, and G. P. Chrousos, “Natural glucocorticoid receptor mutants causing generalized glucocorticoid resistance: molecular genotype, genetic transmission, and clinical phenotype,” *The Journal of Clinical Endocrinology and Metabolism*, vol. 89, no. 4, pp. 1939–1949, 2004.

[68] M. Itoh, M. Adachi, H. Yasui, M. Takekawa, H. Tanaka, and K. Imai, “Nuclear export of glucocorticoid receptor is enhanced by c-Jun N-terminal kinase-mediated phosphorylation,” *Molecular Endocrinology*, vol. 16, no. 10, pp. 2382–2392, 2002.

[69] A. L. Miller, A. S. Garza, B. H. Johnson, and E. B. Thompson, “Pathway interactions between MAPKs, mTOR, PKA, and the glucocorticoid receptor in lymphoid cells,” *Cancer Cell International*, vol. 7, no. 1, p. 3, 2007.

[70] L. B. Li, D. Y. Leung, and E. Goleva, “Activated p38 MAPK in peripheral blood monocytes of steroid resistant asthmatics,” *PLoS One*, vol. 10, no. 10, article e0141909, 2015.

[71] P. J. Chang, P. K. Bhavsar, C. Michaeloudes, N. Khorasani, and K. F. Chung, “Corticosteroid insensitivity of chemokine expression in airway smooth muscle of patients with severe asthma,” *The Journal of Allergy and Clinical Immunology*, vol. 130, no. 4, pp. 877–885 e5, 2012.

[72] P. J. Chang, C. Michaeloudes, J. Zhu et al., “Impaired nuclear translocation of the glucocorticoid receptor in corticosteroid-insensitive airway smooth muscle in severe asthma,” *American Journal of Respiratory and Critical Care Medicine*, vol. 191, no. 1, pp. 54–62, 2015.

[73] A. R. Sousa, S. J. Lane, C. Soh, and T. H. Lee, “In vivo resistance to corticosteroids in bronchial asthma is associated with enhanced phosphorylation of JUN N-terminal kinase and failure of prednisolone to inhibit JUN N-terminal kinase phosphorylation,” *The Journal of Allergy and Clinical Immunology*, vol. 104, no. 3, pp. 565–574, 1999.

[74] C. Wang, J. Luo, X. Bai et al., “Calycosin alleviates injury in airway epithelial cells caused by PM 2.5 exposure via activation of AMPK signalling,” *Evidence-based Complementary and Alternative Medicine*, vol. 2021, Article ID 8885716, 9 pages, 2021.

[75] Y. Xu, H. Liu, and L. Song, “Novel drug delivery systems targeting oxidative stress in chronic obstructive pulmonary disease: a review,” *Journal of Nanobiotechnology*, vol. 18, no. 1, p. 145, 2020.

[76] Y. Wang, D. Li, L. Song, and H. Ding, “Ophiopogonin D attenuates PM2.5-induced inflammation via suppressing the AMPK/NF-kappaB pathway in mouse pulmonary epithelial cells,” *Experimental and Therapeutic Medicine*, vol. 20, p. 139, 2020.