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The role of fine particulate matter (PM2.5) in asthma pathology

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Abstract: Asthma is a chronic disease of the lungs which affected 45.7 million adults in China. Although some of the asthma cases are inherited, in recent years more attention has been paid to environmental factors, one of which is fine particulate matter ($PM_{2.5}$). $PM_{2.5}$ refers to fine particulate matter with a diameter less than 2.5 micrometers, which is small enough to get deep into the lungs, often inducing a series of pathological reactions. This article reviews important findings and recent progress in biological mechanisms of PM2.5 in the asthma pathology, including immunotoxicity, inflammation, oxidative stress, airway remodeling and airway hyperresponsiveness. This review may provide a basis for improved asthma control as well as asthma prevention from a mechanistic perspective.

Keywords: asthma pathology; activities; particulate matter; biological mechanisms

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1. Introduction

Asthma is a chronic disease of the lungs, which causes many respiratory symptoms, including wheezing, breathlessness, chest tightness, and nighttime or early morning coughing[1]. According to the most recent data published on the Lancet, asthma affected 45.7 million adults aged 20 years or older in China, which renders the prevalence of asthma 4.2% high[2].

Although asthma has been proved to be linked with genetic and epigenetic factors, in recent years many researchers have paid more attention to the environmental factors that contributes to the progress of asthma, and a great number of large-scale epidemiological studies have revealed an association between air pollution and asthma attacks[3-6]. Many environmental factors have been identified as asthma triggers, such as tobacco smoke, house dust, pollen, pets, etc.[7, 8]. Among all these triggers, however, $PM_{2.5}$ draws more attention for its unique aerodynamic and toxicological properties.

Although epidemiological studies have provided strong evidence concerning the effect of $PM_{2.5}$ exposures on asthma prevalence and morbidity, the underlying mechanisms remain to be further clarified. This article aims to summarize the role of fine particulate matter in asthma pathology, providing basis for the asthma control and prevention.

1.1 Definition, Sources, and Components of $PM_{2.5}$

As defined by the U.S. EPA, particulate matter (PM) refers to "a mixture of solid particles and liquid droplets found in the air"[9]. PM is classified into different categories based on diameter. $PM_{2.5}$, for instance, stands for fine particulate matter with a diameter less than 2.5 micrometers, which is small enough to get into the lungs and even into the bloodstream, posing potentially great health risks. Both natural and human activities can generate $PM_{2.5}$. Specifically, natural phenomena such as wildfires, volcanoes, and land dust are considered natural sources for $PM_{2.5}$. However, human activities are deemed to be main contributors, the main sources of $PM_{2.5}$ include oil dust, coal combustion, biomass burning, traffic emission and industrial pollution[10].

The chemical composition of $PM_{2.5}$ is a key factor in the ultimate health effects of $PM_{2.5}$. The components may vary in different areas and times, with different amounts of organic matter, sulphate, crustal material, nitrate, or ammonia[11]. According to a recent study in two cites in China, secondary inorganic aerosol (SNA) and organic matter (OM) are the dominant components in the total concentration, but significant seasonal variations were observed in the chemical composition, with the highest mass concentration in winter and the lowest in summer[12]. A study in Malaysia also showed that meteorological and gaseous parameters vary greatly with different seasons which has a great impact on the chemical constituents and sources of $PM_{2.5}$. Also, the overall $PM_{2.5}$ concentrations were shown to rise with higher temperatures, greater wind speed, and lower relative humidity[13].

1.2 Particle Deposition in Airways

Every day people inhale millions of particles, but not every of them will deposit in human respiratory tract. Factors such as size, density, shape, charge, and surface properties can all affect the deposition of particles, but most particles are deposited depending on their size[14]. Total deposition rate in the respiratory tract is different for particles with different

diameters; also, the major mechanisms of their final deposition can vary.

For oral breathing, the deposition patterns of different particles are characterized by three domains. Particles with diameters less than 0.1μm are deposited only by diffusion, which is called the thermodynamic domain. In this domain, the total deposition decreases as the diameter of the airspace increases. For larger particles, gravity plays a more important role, leading to the intermediate domain. In the intermediate domain, particles are impacted by both gas composition and gravity. The intermediate domain continues up to a diameter of about 1μm, when inertial transport becomes an important mechanism. Particles with diameters between 1μm and 10μm are deposited due to impaction and sedimentation, forming what is called the aerodynamic domain, and the total deposition increases with larger diameters[14, 15]. For nasal breathing, the intermediate domain disappears but the total deposition similarly first decreases and then increases as the diameter increases [15].

Different particles also tend to be deposited in the different parts of the respiratory tract. Take steady nasal breathing as an example. In such case, smaller particles (<1μm) are more likely to be deposited in the deeper parts of the lungs while larger particles mostly are deposited in the nose due to inertial impaction [16]. Kreyling also found more nanoparticles relocated into pulmonary tissues compared to larger ones after a twelve-week exposure [17]. More importantly, particles with diameters between 2.5-10 μm deposit in the trachea and bronchi, most of which can be removed in the sputum; on the other hand, $PM_{2.5}$ particles tend to go deep into the distal airways and alveoli, where they can't be removed by mucociliary clearance itself. Thus $PM_{2.5}$ particles can stay in the alveoli, subsequently provoking a series of pathological reactions[18].

1.3 Epidemiological studies on $PM_{2.5}$ effects on asthma

A large portion of research has focused on the PM effects in children, and the results have demonstrate that elevated $PM_{2.5}$ levels are related to the development and exacerbation of child asthma[19, 20]. In an investigation in inner-city Baltimore, a 10 μg/m^3 increase in particle concentration was found to increase asthma symptoms by 7 to 14%, as well as in incease in rescue medication among both non-atopic and atopic children[21]. A bidirectional case-crossover study in Turkey examined the association between various particulate matter ($PM_{2.5}$, $PM_{10-2.5}$, and PM_{10}) and children asthma hospital admissions, the results of which showed a 1.15 odds ratio for an increase of 10 μg/m3 in $PM_{2.5}$ concentrations. Another study also suggested that $PM_{2.5}$ can have a greater effect on children's hospital admissions for asthma compared with PM_{10} [22].

As for adults, most previous studies also have reported consistent results showing that increases in $PM_{2.5}$ concentrations can exacerbate asthma attacks. In a 2016 paper, which included 50356 adults with active asthma, results showed that a 14-day average $PM_{2.5}$ greater than 7.07 μg/m3 was related to a 4–5% higher asthma symptom prevalence, and further that in the range of 4.00–7.06 μg/m^3, each 1 μg/m^3 $PM_{2.5}$ increase was related to a 3.4% increase in asthma symptom prevalence[23]. Similarly, a Spanish cohort study also demonstrated the role of traffic-related pollution in adult-onset asthma among never-smokers with the hazard ratio of 1.30 per μg/m^3[24]. However, a US study using two national datasets did not find significant difference with a 10 μg/m^3 increase in $PM_{2.5}$ among the overall population; but after stratified by race/ethnicity, significant relationships were shown for non-Hispanic blacks with an odds ratio of 1.73 for current asthma and an odds ratio of 1.76 for recent attacks[25].

2. Biological mechanisms of $PM_{2.5}$ Effects

2.1 Immunotoxicity

$PM_{2.5}$ can cause adverse health effects in different organs, where immunotoxicity can play an important role. Their sticky porous surfaces as well as static electric charges enable theses particles to absorb free allergens in the air released from animals, dust mites, mold, and pollen[26]. Therefore, small particles carrying airborne allergens serve as transporters and bring the allergens deep into human respiratory system, causing allergic responses. It was demonstrated that the particulate-bound allergens triggered significantly more severe asthma symptoms in allergen-sensitized mice compared with soluble allergens[27].

Many studies have demonstrated that the exposure of particulate matters can break the balance of Th1/Th2 by activating Th2 and deactivating Th1 [28-30]. In asthmatic groups, increased levels of Th2-realted cytokines IL-4, IL-5, IL-10, IL-13 were observed while the levels of Th1-realted cytokines INF-γdecreased, indicating $PM_{2.5}$ drives a Th2-biased immune response [29, 30]. Meanwhile, $PM_{2.5}$ exposure induced high levels of serum immunoglobulins, especially IgE[30, 31]. In Wang's study, the total serum IgE level in the exposed group was increased by 1.62 fold compared to the control group while the IgG level also moderately increased [30]. Thus IgE-dependent hypersensitivity occurred, mediated by Th2. Notably, Castañeda also proved PM alone could enhance IgE levels without carrying allergens, which is consistent with Diaz-Sanchez's study[32].

Nevertheless, imbalance of Th1/Th2 cannot account for all the asthmatic symptoms. In recent years, an important role of differentiated Th17 T cells has been shown. Th17 is a CD4+ helper T cell which produces

IL-17, TNF-α, Iymphotoxin-β, and IL-22 when activated [33]. Studies suggested PM exposure could induce more severe Th17-mediated lung inflammation with increased levels of Th17-related cytokines and transcription factors found in exposed groups[34,35]. Th17 cytokines enhance allergic response by neutrophil accumulation and mucus secretion, and narrow airway by promoting airway smooth muscle cell proliferation[36]. Asthma patients with increased IL-17 and neutrophils were found to have the worst asthma control[37].

2.2 Inflammation

Upon inhalation into the body, $PM_{2.5}$ will eventually deposit in the alveoli if the particles can get through the mechanical defenses, such as the nasal passages, the glottis, and the mucus layer on airways. Once the particles settle, they encounter an immediate cellular defense mechanism – the resident macrophages. These macrophages, as known as dust cells, are the primary phagocytes of the innate immune system located near the pneumocytes in the alveoli. The alveolar macrophages ingest foreign particles through phagocytosis and they also can secrete oxygen metabolites, lysozymes, antimicrobial peptides and proteases to kill microorganisms absorbed on the particle surface[38]. When stimulated by $PM_{2.5}$, airway epithelial cells also produce a great amount of cytokines including IL-6, IL-8, TNF-α, TGF-β1, etc.[39]. Simulataneously, IL-5 and chemotactic factors are released from the mast cells during Type I hypersensitivity, causing airway accumulation of eosinophils, which enhances airway inflammation[40,41]. Eosinophils play an important role in the inflammatory response. The release of granule-associated basic proteins leads to increased vascular permeability, epithelial damage, contraction of smooth muscle, and elevated secretion of mucus. IL-5 increases eosinophils by mediating proliferation, differentiation, migration, and survival[42].

A great number of experimental studies support the theory of increased inflammatory cells after $PM_{2.5}$ exposure. A recent study in China found more severe inflammatory cell infiltration in the peribronchial and perivascular regions in $PM_{2.5}$-exposed asthmatic mice compared with unexposed asthmatic mice. The exposure to $PM_{2.5}$ increased the number of both eosinophils and neutrophils by about 2-fold. The difference was no longer significant when a particle filter was used in the exposed group[30]. In addition to the lungs, more inflammatory cells were found in the nose as well. A French study conducted in 2006 examined the numbers of neutrophils and eosinophils in the nasal lavage of asthmatic children and healthy children, showing that exposure to $PM_{2.5}$ was significantly related to the percentage of eosinophils. The number of neutrophils also increased, but no significant difference was found[43]. Chen's research came up with similar results, indicating that $PM_{2.5}$ levels increased leukocytes by 3.51% and neutrophils by 3.45%, but neither of the two results were significantly different [44]. What's more, it is worth noting that the composition of $PM_{2.5}$ could have an impact on the proliferation of the inflammation cells. In a 2003 study, $PM_{2.5}$ samples from two areas were collected and administered to ovalbumin-allergic mice. With similar $PM_{2.5}$ concentrations, significant increases of lung inflammatory cells were only observed in mice exposed to $PM_{2.5}$ which had several-fold higher levels of lead, copper, cadmium, and tin, despite the fact both groups had significant increased proinflammatory cytokines compared to the control group[45].

The expression of inflammatory genes was also studied. According to a recent study in Japan, significantly increased levels of interleukin-1β (IL-1β) and cyclooxygenase-2 (Cox2) were observed in mouse macrophages after exposure to $PM_{2.5}$ at different concentrations in a dose-response manner. The results also showed a peak at 3 hours for these effects. Notably, the increases of IL-1β and Cox2 levels not present after $PM_{2.5}$ particles were heated at 360°C, indicating compounds absorbed on the particle surface contributed to the induction of inflammatory gene expression[46]. He's research confirmed the induction of proinflammatory mediators by $PM_{2.5}$. The $PM_{2.5}$ exposures caused significant increased expression of MCP-1, MIP-1α, TNF-α and COX2 genes in the macrophage cell line compared with controls, and was strongly attenuated by polymyxin B[47].

The inflammation response involves several pathways. The activation of NF-kB was found to play the most important role. In Bekki's study which was mentioned above, the increases of IL-1β and Cox2 genes were nearly suppressed with the NF-kB inhibitor BAY 11-7085, indicating the NF-kB is the main pathway for $PM_{2.5}$-induced inflammatory reaction[46]. Song's study further demonstrated that $PM_{2.5}$ exposure reduced miR-331 expression in human airway epithelial cells via ROS/PI3K/Akt pathways and that down-regulated miR-331 expression activated the NF-kB pathway[48]. The exposures of PM2.5 also enhanced the MAPK pathways including p38 MAPK, extracellular response kinases (ERK), and Jun N-terminal kinase (JNK), which could also be suppressed by polymyxin B[47].

The role of endotoxin was investigated as a cytokine-inducing moiety in the inflammatory response. Endotoxin is contained within the outer membrane of gram-negative bacteria and released when the cell disintegrates. Endotoxin contributes to the inflammatory reaction by upregulating TNF-α, IL-1 and IL-6. After treatment with an endotoxin neutralizer, PM2.5 generated significantly lower levels of IL-1 β and Cox2[46, 49]. As a matter of fact,

endotoxin is not uncommon in $PM_{2.5}$, and a high concentration of 0.107ng/mg was detected in Bekki's study.

2.3 Oxidative Stress

The deposition of $PM_{2.5}$ in the airway can lead to the release of reactive oxygen species (ROS) from bronchial epithelial cells, which promotes cellular oxidative stress[50]. Higher inflammation and oxidative stress and worsened lung impedance were all observed with higher levels of $PM_{2.5}$ exposure[51]. Lakey et al. found the ROS concentrations induced by $PM_{2.5}$ with concentrations over 50μg/m^3 were around 100-250 nmol/L in healthy persons, which reached the levels of patients with acute inflammatory respiratory diseases[52]. On the other hand, alveolar macrophages can also produce ROS/RNS after PM phagocytosis. NADPH oxidase Nox complex may be involved in this progression, which was found to be increased after PM exposure[53]. Catalyzed by activated NOx, electrons transfer from cytosolic NADPH to molecular O_2 across the membrane, where superoxide radicals are produced [54].

Similarly, the chemical composition of $PM_{2.5}$ also influences the amount of ROS induced, which has been proved by several studies. The results from Yang et al. showed that different high levels of ROS were produced with different sources of $PM_{2.5}$. The Fe element generated the highest levels of ROS while PAHs and Ni element were significantly related to the overexpression of IL-1β and high apoptosis rates[55]. Lakey et al. used a kinetic multi-layer model of surface and bulk chemistry to examine the ROS production rates generated by different air pollutants in the epithelial lining fluid. Apart from the finding that the ROS production increased in response to higher concentrations of $PM_{2.5}$ (10nmol/L in the cleanest air, and up to 250 nmol/L in the highly-polluted air), different rates of ROS production were observed for each pollutant. Cu and Fe ions were found to induce the highest levels of ROS, followed by quinones and SOA. The ROS level would decrease by 10% in the moderately-polluted air with the removal of Fe. This is because Fe plays an important role in the catalysis of H_2O_2 to OH radicals, and thus the removal of Fe ions is critical for reducing oxidative stress resulted from OH radicals[52].

Oxidative stress leads to inflammatory gene expression with a subsequent inflammation response. Data have indicated that both water-soluble and non-soluble particles are able to induce IL-8 expression, which is an inflammatory mediator[51]. Higher levels of proinflammatory mediators were found together with decreased activities of total superoxide dismutase (T-SOD)[56]. PM-induced oxidative stress was also related to the increase of activated dendritic cells, which results in a greater Th2 lypmphocyte response [57]. Furthermore, intracellular signaling cascades can be induced by an imbalance of the oxidant production, which leads to oxidative damage to cellular and mitochondrial macromolecules [53]. A recently published study observed decreased mitochondrial membrane potentials and damaged mitochondrial membrane integrity caused by excessive ROS via this oxygen-dependent killer route. Mitochondrial damage triggers cell apoptosis and causes damage to the lungs, resulting in even further worsening of asthma symptoms[58].

$PM_{2.5}$-induced ROS production can be inhibited by serum- and glucocorticoid-inducible kinase 1(SGK1) [59]. SGK1 is found to be a kinase that promotes cell survival and suppresses apoptosis in tumor cells[60]. The protective role of SGK1 in reducing ROS has been demonstrated in human lung alveolar epithelial cells. A significant decrease in ROS production was observed with the overexpression of SGK1[56].

2.4 Airway remodeling and airway hyperresponsiveness

Asthma is characterized by airway remodeling and airway hyperresponsiveness (AHR), and $PM_{2.5}$ exposure was found to have effect on both features. Airway remodeling refers to airway structural changes attributed to chronic inflammation, including subepithelial fibrosis, increased smooth muscle mass, enlargement of glands, neovascularization, and epithelial alterations[61]. A study conducted in Mexico City, a high PM area, examined histologic sections from the lungs of 20 local people and then compared them with non-exposed people in Vancouver. Abnormal small airways with thicker fibrotic walls and excess muscle were found both in the membranous bronchioles (MBs) and respiratory bronchioles (RBs) of the Mexico City lungs[62].

Studies have suggested, inflammatory factors, such as transforming growth factor-β1 (TGF-β1), are able to induce the differentiation of fibroblasts into myofibroblasts with α-Smooth muscle actin. Myofibrobalsts over synthesize and secrete extracellular matrix (ECM) proteins, thickening and stiffening the extracellular basement membrane[63].

Airway hyperresponsiveness refers to exaggerated bronchoconstrictor response to various stumuli, causing airway narrowing with overcontraction of airway smooth muscle[64]. Several studies have demonstrated effects of PM2.5 on AHR. Exacerbated AHR was observed with $PM_{2.5}$ exposure, either provoked by Acetylcholine or Methacholine[28, 30]. Archer's study strongly supported the importance of PM exposure, showing that increases AHR occur in a dose-dependent manner to increases in PM[65]. T lymphocytes may play a role in PM-induced AHR, as increased bronchoalveolar lavage fluid lymphocytes, eosinophils, neutrophils, and mucus-containing cells

were found in the lungs after exposure[66].

3. Conclusion

This essay focuses on the biological and mechanistic effects of $PM_{2.5}$ in asthmatic populations throughout the world. With its small particle diameter, $PM_{2.5}$ can go deep into the respiratory track and deposit in the alveoli, subsequently leading to a series of harmful pathological reactions. The main mechanisms of these adverse health effects involve inflammation and oxidative stress, which lead to the overexpression of inflammatory genes, and the inflammatory cytokine expression serves to mediate the airway remodeling and airway hyperresponsiveness.

Air pollution remains one of the biggest challenges the world is facing, especially for developing countries. Further study is needed to clarify the effects of air pollution in the progress of different diseases. More importantly, in terms of primary prevention, efforts should be made to alleviate air pollution and reduce human exposures.

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