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Perspective

Effects of particulate matter on allergic respiratory diseases

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Abstract

The health impact of airborne particulate matter (PM) has long been a concern to clinicians, biologists, and the general public. With many epidemiological studies confirming the association of PM with allergic respiratory diseases, an increasing number of follow-up empirical studies are being conducted to investigate the mechanisms underlying the toxic effects of PM on asthma and allergic rhinitis. In this review, we have briefly introduced the characteristics of PM and discussed its effects on public health. Subsequently, we have focused on recent studies to elucidate the association between PM and the allergic symptoms of human respiratory diseases. Specifically, we have discussed the mechanism of action of PM in allergic respiratory diseases according to different subtypes: coarse PM ($PM_{2.5\text{-}10}$), fine PM ($PM_{2.5}$), and ultrafine PM.

Keywords: Particulate matter; Allergic respiratory diseases; Coarse PM; Fine PM; Ultrafine PM

Physical and chemical characteristics of particulate matter

The growing population density and the rapid urbanization lead to the deterioration of air quality worldwide, especially in China.[1] Atmospheric particulate matter (PM; pl. "particulates"), consisting of both primary and secondary particles, is one of the major air pollutants. Primary PM is generated from road transport, combustion (mainly coal burning), and other industrial processes, whereas secondary PM is generated through chemical reactions among different primary particulates in the atmosphere (e.g., sulfates

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and nitrates, formed from the conversion of SO_2 and NO_2 into their respective acids).[2]

Particulates are classified into three categories according to their aerodynamic diameters: coarse PM ($PM_{2.5-10}$, aerodynamic diameter ranging from 2.5 to 10 μm), which deposits primarily in the primary bronchi[2]; fine PM ($PM_{2.5}$, ranging from 0.1 to 2.5 μm), which can penetrate the alveoli and terminal bronchioles[2]; and ultrafine PM ($PM_{0.1}$ or UFP, less than 0.1 μm), which can cross cell membranes and interact directly with cellular structures.[3,4]

PM toxicity arises from two aspects. First, the particulates can penetrate the gas-exchange region of the lung and thereby infiltrate the circulatory system through layers of alveolar obstruction.[5,6] Second, particulates can absorb many other airborne toxic substances on their surface area, such as heavy metals, polycyclic aromatic hydrocarbons, and organic and inorganic ions.[7]

PM as a risk factor to public health

PM has become a public health concern, having being implicated as the cause of 4.24 million deaths in 2015, 7.8% higher than that in 2005.[8] In 2015, PM ranked 6th on the list of 10 most hazardous factors contributing to global disability-adjusted life-years.[8] Many epidemiological studies worldwide have addressed the correlation between the concentrations of PM and hospital visits due to respiratory diseases (Table 1).[9–16]

PM interacts directly with the human body. Although particulates can be detected in many organs such as the lungs, liver, kidneys, heart, and brain, their deposition patterns show that lungs are the primary site.[17] Because of the heterogeneity in their chemical and physical properties, there is no standard toxic dose for PM. According to Fann et al,[18]even exposure to PM at a concentration below the US national standards poses a significant risk to health.

Because of its substantial health impacts, the World Health Organization Air Quality Guidelines (WHOAQG) have established $PM_{2.5}$ as the indicator of pollution caused by particulates in 2006.[7]

Effects of PM on allergic respiratory diseases

Asthma and allergic rhinitis (AR) are the major types of allergic respiratory diseases, characterized by their similar pathophysiological changes and inflammatory responses.[19] The major risk factors of allergic respiratory diseases are genetic (germline risk loci) and environmental factors (including PM).[20] Although many studies have confirmed that exposure to particulates has significant effects on asthma and AR, the mechanism by which PM influences these diseases is not fully understood. In the following sections, the latest advances that have helped in elucidating the pathogenicity of different PM subtypes are summarized (Fig. 1).

Coarse PM ($PM_{2.5-10}$)

Coarse PM is deposited in extra thoracic airways and induces various symptoms of pulmonary inflammation.[2] Studies have shown the pulmonary toxicity of coarse PM both *in vivo* and *in vitro*.[21–23] We discuss three detailed mechanisms of such toxicity induced by coarse PM (Fig. 1A,B, and E) below.

$PM_{2.5-10}$ activates neutrophils and eosinophils

Diesel exhaust particles (DEPs), a type of coarse PM, exacerbate the symptoms of AR by increasing the levels of the proinflammatory cytokines interleukin (IL)-8, IL-1β, granulocyte-macrophage colony stimulating factor (GM-CSF), and tumor necrosis factor-alpha (TNF-α) in nasal epithelial cells.[24,25] Terada et al[26] claimed that DEPs activate proinflammatory cytokines by upregulating histamine H1 receptor (H1R) expression. The proinflammatory cytokines further induce neutrophils and eosinophils, leading to inflammatory responses.[27] In addition, $PM_{2.5-10}$ was shown to increase the number of IL-5-induced eosinophils in exposed allergic mice.[27]

$PM_{2.5-10}$ induces antigen-presenting cell-mediated inflammatory responses

Becker et al[4] demonstrated that $PM_{2.5-10}$ modulates airway macrophage host defenses by significantly increasing IL-6 levels and suppressing cluster of differentiation (CD) $11b^+$ macrophages in human alveoli. In asthmatic patients exposed to $PM_{2.5-10}$, an inflammatory response was observed with decreased expression of the innate immune receptors CD11b/complement receptor 3 (CR3) and CD64/FcγRI, and the antigen-presenting receptors CD40 and CD86/B7-2, and concomitantly increased expression of the inflammatory receptor CD16/FcγRIII and the low-affinity IgE receptor CD23 in macrophages.[28] DEPs induced murine dendritic cell activity, causing their migration to the mediastinal lymph node, which strengthened the immune response via the nuclear factor-erythroid 2-related factor 2 (Nrf2) signaling pathway.[29]

Table 1
Representative epidemiological studies of the association between particulate matter concentrations and hospital visits due to respiratory diseases.

References	Study	Location	Time	PM	Analysis methods	Population	Diseases	Findings	*RR/OR/IR* (95% *CI*)
9	Impact of PM on human health within the urban environment	Athens, Greece	2001−2013	PM_{10}	AirQ2.2.3 model	All ages	HARD	A strong relationship between the HARD cases and PM_{10} exposure levels	−
10	Effects of PM on respiratory disease	Busan, Korea	2007−2010	$PM_{2.5}$ PM_{10}	Multivariate analysis	All ages	HARD	A significant increase in HARD with increasing PM levels	*RR*: 1.008 (1.007−1.009) *RR*: 1.003 (1.003−1.004)
11	Associations between air pollutants and pediatric asthma hospital admissions	New York, USA	1999−2009	$PM_{2.5}$	Generalized additive models	6−18 years	Asthma HAs	$PM_{2.5}$was statistically significantly associated with increased asthma HAs	*RR*: 1.02 (1.00−1.04)
12	Correlation between air pollution and children's asthma-related emergency hospital visits	Southeastern France	2013	PM_{10}	Nested case−control study	3−18 years	Children's asthma ERVs	PM_{10} near children's homes increased the risk of asthma ERVs	*OR*: 1.02 (1.01−1.04)
13	Correlation between PM_{10}/$PM_{2.5}$ and outpatient visits for respiratory disease	Jinan, China	2013−2015	$PM_{2.5}$ PM_{10}	Generalized additive model	All ages	Respiratory diseases	Ambient PM_{10} and $PM_{2.5}$ pollution was positively associated with daily hospital visits due to respiratory disease	*IR*: 0.36% (0.30%−0.43%) *IR*: 0.50% (0.30%−0.70%)
14	Effects of fine PM on emergency room visits for asthma	Southern Taiwan, China	2008−2010	$PM_{2.5}$	Quasi-Poisson generalized additive model	Children	Hospital ERVs for asthma	Children were susceptible to the effects of $PM_{2.5}$	*RR*: 1.016 (1.002−1.030)
15	Effects of exposure to indoor PM on symptoms and acute exacerbations in COPD patients	Southwestern Taiwan, China	2014−2016	PM_{10}	Generalized estimating equation analysis	All ages	Admission due to acute exacerbation of COPD	PM was associated with worse respiratory symptoms and increased risk of COPD exacerbation in patients with moderate to very severe COPD	*OR*: 16.2 (3.10−84.9)
16	Correlation between fine particulate air pollution and hospital visits for asthma	Beijing, China	2010−2012	$PM_{2.5}$	Generalized additive Poisson model	All ages	Asthma HVs Asthma OVs Asthma ERVs	Short-term elevations may increase the risk of asthma exacerbation	*IR*: 0.67% (0.53%−0.81%) *IR*: 0.65% (0.51%−0.80%) *IR*: 0.49% (0.35%−0.64%)

PM: particulate matter; *RR*: relative risk (the relative risk of increased hospital visits with a 10 $\mu g/m^3$ increment of PM); *OR*: odds ratio; *IR*: increase ratio (the increase ratio of hospital visits with a 10 $\mu g/m^3$ increment of $PM_{2.5}$); *CI*: confidence interval; HARD: hospital admissions for respiratory diseases; HAs: hospital admissions; ERVs: emergency room visits; COPD: chronic obstructive pulmonary disease; HVs: Hospital visits; OVs: Outpatient visits; −: not applicable.

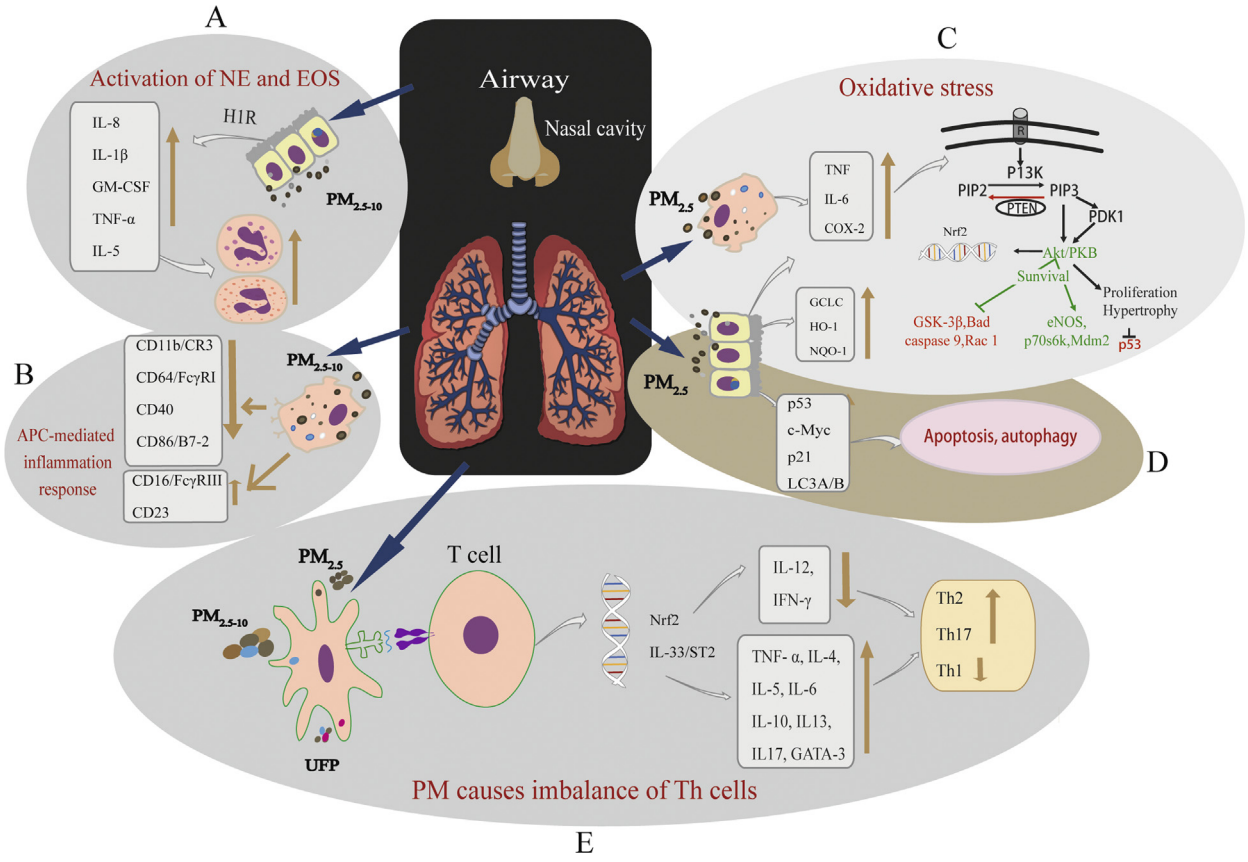

Fig. 1. Different pathways of PM toxicity and their mechanisms in allergic respiratory diseases. (A) $PM_{2.5\text{-}10}$ activates neutrophils and eosinophils; (B) $PM_{2.5}$ induces antigen-presenting cell-mediated inflammatory responses; (C) $PM_{2.5}$ induces oxidative stress; (D) $PM_{2.5}$ leads to apoptosis and autophagy; and (E) $PM_{2.5}$ causes imbalance of T helper cells. PM: particulate matter; NE: neutrophils; EOS: eosinophils; IL: interleukin; H1R: H1 receptor; GM-CSF: granulocyte-macrophage colony stimulating factor; TNF: tumor necrosis factor; COX-2: cyclooxygenase-2; PI3K: phosphatidylinositol-4,5-bisphosphate 3-kinase; PIP2: phosphatidylinositol (4,5)-bisphosphate; PIP3: phosphatidylinositol (3,4,5)-trisphosphate; PTEN: phosphatase and tensin homolog; NrF2: nuclear factor (erythroid-derived 2)-like 2; PDK1: phosphoinositide-dependent kinase-1; Akt: protein kinase B; PKB: protein kinase B; GCLC: glutamate-cysteine ligase catalytic subunit; HO-1: heme oxygenase-1; NQO-1: NADPH quinone oxidoreductase; GSK-3β: glycogen synthase kinase-3 beta; Caspase: cysteine aspartic acid protease; Rac1: ras-related C3 botulinum toxin substrate 1; p70s6k: p70 ribosomal protein S6 kinase; mdm2: Mouse double minute 2 homolog; APC: antigen-presenting cell; CD: cluster of differentiation; CR3: complement receptor 3; LC3A/B: light chain 3A/B; IFN-γ: interferon-gamma; ST2: IL-33 receptor; Th: T-helper; UFP: ultrafine particulate matter.

$PM_{2.5\text{-}10}$ induces T-helper (Th)2- and Th17-mediated immune responses

DEP was shown to induce a Th2-mediated immune response by suppressing the expression of IL-12 and interferon-gamma (IFN-γ), and increasing IL-10 secretion in antigen-specific T cells.[29] Similarly, Chan et al[29] reported that DEPs provoke a Th2-mediated immune response in asthmatic mice by increasing IL-10 secretion in lipopolysaccharide-induced antigen-specific T cells through the Nrf2 signaling pathway. Co-exposure to DEPs and home dust mites induced allergen-specific Th2 and Th17 cells via the IL-33/ST2 (IL-33 receptor) pathway in the lungs of PM-exposed asthmatic mice.[30,31] The same responses could be triggered by co-exposure of DEP with a low level of soybean allergen.[32]

Inflammatory responses cause a series of pathological changes in allergic respiratory diseases. Kobayashi et al[33] determined that DEPs cause a severe nasal allergic reaction in AR mice. Guinea pigs exposed to DEPs displayed symptoms of nasal mucosal hyperresponsiveness.[34,35]

The aforementioned immune activities of $PM_{2.5\text{-}10}$ arise from the enriched heavy metal constituents, more biogenic materials with higher endotoxin contents, and other toxic absorbents, which lead to a stronger short-term effect on respiratory diseases compared with other PM subtypes.[36–39]

Fine PM ($PM_{2.5}$)

Unlike $PM_{2.5-10}$, $PM_{2.5}$ is not only deposited in extra thoracic airways but also penetrates deeper and farther into the alveoli through air flow and diffusion.[40] Hence, $PM_{2.5}$ can induce various symptoms of pulmonary inflammation and structure impairment (Fig. 1C−E).[40]

$PM_{2.5}$ causes imbalance of T helper cells

High concentrations of $PM_{2.5}$ upregulate TNF-α and the Th2-mediated cytokines IL-4 and IL-10, while downregulating the Th1-mediated cytokine IFN-γ, which leads to an imbalance of the Th1/Th2 ratio.[41,42] $PM_{2.5}$ was shown to significantly increase the expression of IL-13 and IL-17.[42] In a study on rats with AR, the authors pointed out that the expression of IFN-γ, IL-4, IL-5, IL-33, intercellular adhesion molecule 1 (Icam1), and vascular cell adhesion molecule 1 (Vcam1) was increased in a $PM_{2.5}$ concentration-dependent manner.[43] High expression levels of INF-γ, IL-4, and IL-13 were also seen in the nasal lavage fluid. The Th1/Th2 imbalance was mainly driven by the activation of GATA binding protein 3 (Gata3) and the suppression of T-box 21 (T-bet) in AR rats.[44−49] Liu et al[50] showed that $PM_{2.5}$ exacerbates asthma by activating the expression of transient receptor potential cation channel, subfamily A, member 1 (Trpa1) and transient receptor potential cation channel, subfamily V, member 1 (Trpv1) protein in the epithelial cells of asthmatic mice. Thus, high concentrations of $PM_{2.5}$ promote Th2-and Th17-mediated immune responses in AR and asthmatic mice.[41,42,51−53]

Following exposure to $PM_{2.5}$, the lungs exhibit a series of pathological changes, such as inflammatory cell infiltration, bronchial smooth muscle thickening, and bronchial mucosal injury in asthmatic mice.[50] $PM_{2.5}$ treatment of rats with ovalbumin (OVA)-induced AR resulted in increased sneezing and nose scratching events, with goblet cell hyperplasia and collagen deposition in the pathological state.[44]

$PM_{2.5}$ induces oxidative stress in asthma

Exposure to $PM_{2.5}$ is associated with oxidative stress and impaired lung function.[54−56] A burst of reactive oxygen species induced by $PM_{2.5}$ was found in the neutrophils of asthmatic patients.[57] Deng et al[58] reported that $PM_{2.5}$ induces oxidative stress by increasing the expression of glutamate-cysteine ligase catalytic subunit (GCLC), heme oxygenase-1 (HO-1), and NADPH quinone oxidoreductase (NQO-1)in human lung epithelial cells (A549), and thereby activates Nrf2 in the phosphatidylinositol-4,5-bisphosphate 3-kinase (PIK3)/AKT signaling pathway. Huang et al[59] reported that water-soluble $PM_{2.5}$ (WSPE) induced an oxidative stress response in A549 cells. Becker et al[60] revealed that $PM_{2.5}$ induces oxidative stress responses by inducing TNF-α, IL-6, and cyclooxygenase-2 (COX-2) expression in alveolar macrophages and human bronchial epithelial cells.

$PM_{2.5}$ leads to apoptosis and autophagy in asthma

Exposure to $PM_{2.5}$ can also induce apoptosis and autophagy. WSPE induced apoptosis in lung epithelial cells through the p53, c-Myc, and p21 signaling pathways.[59] The particulates also caused cell autophagy through upregulation of LC3A/B (biomarkers of autophagy) in asthmatic mice.[42] Deng et al[61] reported that $PM_{2.5}$ induces apoptosis and autophagy via three pathways in human lung epithelial cells: the TNF-α signaling pathway; the intrinsic apoptosis pathway via caspase-8 and caspase-3 signaling; and the cell autophagy pathway via caspase-9,caspase-3,and B-cell lymphoma 2 (BCL2).

UFP

With an even smaller size, UFP can cross cell membranes and directly interact with cellular structures,[3,4]potentially posing a high risk of respiratory disease development (Fig. 1E).[62]

UFP causes severe inflammation in asthma

UFP can escape mucociliary clearance and ingestion by alveolar macrophage scavenging.[62] One study detected UFP in the blood immediately after inhalation, and the particulates remained in the lungs for up to 6h after installation.[63] Therefore, UFP can induce severe eosinophilic inflammatory responses, alveolar macrophage chemotaxis, and more epithelial damage *in vivo*.[64,65]

UFP induces Th2-mediated inflammation

In OVA-sensitized mice, UFP promoted the proliferation of peribronchial lymph node cells and caused a Th2-mediated immune response[66,67] by activating the cytokines IL-4, IL-5, IL-10, and IL-13.[66] IL-5 and IL-6 were also shown to be significantly increased in the bronchoalveolar lavage fluid of UFP-exposed mice.[4,27,68]

In another study, a high dose of ultrafine carbon black particles or ultrafine TiO_2 particles, co-exposed with OVA, led to a high level of OVA-specific IgE in asthmatic mice.[67] Ultrafine CeO_2 particles (produced by motor vehicle combustion) significantly increased the levels of TNF-α and IL-1β as well as neutrophils in exposed mice.[17]

Summary and perspectives

In summary, PM triggers a series of biological processes including innate immunity inflammation, oxidative stress, apoptosis and autophagy, and an imbalance of T helper cells, all of which are associated with pathological changes in allergic respiratory diseases.

It is well known that particulates of different aerodynamic diameters and chemical compositions can result in different inflammatory responses in the respiratory tract.[68] Detailed mechanistic studies on the effects of PM exposure are required, although development of T-helper cell imbalance seems to be a common effect of these PM particles (Fig. 1E). Moreover, there is currently no clinical consensus on the prevention or treatment of allergic symptoms associated with PM. Thus, the mechanisms underlying the interaction between PM and the immune system still need to be elucidated and addressed clinically.

Furthermore, the biological effects of particulates are based on their chemical compositions, which vary substantially with the sources of pollution. Future studies on the chemical profiles of different particulates and their corresponding biological impacts should provide insights into their toxicology and information on the clinical treatment of allergic respiratory diseases caused by them.

Conflicts of interest

All authors have no conflicts of interest to disclose. The authors alone are responsible for the content and writing of the paper.

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