Biological Mechanisms of Respiratory Effects of Particulate Matter and its Interaction with COVID-19

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Abstract

Particulate matter (PM) is an aggregate of particles and chemical/biological components. Some of these components include harmful substances, and fine PM easily reaches the bronchioli and alveoli when inhaled, causing health challenges in the respiratory and immune systems. Exacerbation of respiratory diseases, such as bronchitis and bronchial asthma, is one of the representative cases. There is also concern that PM exacerbates coronavirus disease 2019 (COVID-19). Here, we introduce the health effects of PM and its components and the underlying mechanisms, focusing on the respiratory and immune systems from the perspective of an experimental approach.

Key words: acquired immune system, allergy, bronchitis, COVID-19, epithelial barrier, innate immune system

1. Effects of PM on the Epithelial Barrier and Innate and Acquired Immune Systems

Air pollutants in the atmosphere surrounding us affect our respiratory and immune systems adversely. Particulate matter (PM) in the atmosphere, especially PM2.5 (particulate matter with aerodynamic diameters ≤2.5 μm), reaches deep into the lungs (Heyder *et al*., 1986). PM2.5 is generated by human activities (combustion, industrial production, etc.) and natural activities (sand dust, volcanic activity, etc.) and contains hydrocarbons, metals, ions, endotoxins and β-glucan (Chowdhury *et al*., 2018). Compared to large particles, PM2.5 easily reaches the bronchioli and alveoli when inhaled, and some of these various components contain harmful substances; therefore, PM2.5 can contribute to respiratory and immune diseases such as bronchitis and bronchial asthma (Ko and Kyung, 2022).

Airway epithelial cells are constantly exposed to environmental contaminants and are the first physicochemical contact point between xenobiotics and the respiratory system. These cells physically remove xenobiotics by mucociliary transport (Fig. 1). The respiratory mucosa also contains antimicrobial peptides and proteins, contributing to bacterial eradication (Beentjes *et al*., 2022). When PM and its components induce damage and inflammation in airway epithelial cells, xenobiotics can easily enter the airway. Phagocytes, including neutrophils and macrophages, and group 2 innate lymphoid cells (ILC2) are activated in innate immunity, while dendritic cells/macrophages that have antigen-presenting abilities and phagocytic functions, lymphocytes including T cells and B cells, along with eosinophils and mast cells are involved in acquired immunity.

Diesel exhaust particles (DEP), representative of PM2.5, and H_2O_2 produced from the photolysis of ozone or ambient PM2.5, have been reported to reduce airway mucociliary motility (Bayram *et al*., 1998; Honda *et al*., 2014) and weaken epithelial tight junctions (Smyth *et al*., 2020; He *et al*., 2021). These are associated with dysfunction of the epithelial barrier. PM2.5 collected from Asian countries, such as Japan, Bangkok, Taiwan and Singapore, induces the release of pro-inflammatory molecules such as interleukin (IL)-6 or IL-8 from airway epithelial cells (Chowdhury *et al*., 2019, Honda *et al*., 2022). IL-6 and IL-8 play important roles in inflammation of the respiratory system by inducing neutrophil recruitment, up-regulating mucin secretion and stimulating lymphocytes (Bautista *et al*., 2009; Chen *et al*., 2003; Levine *et al*., 1993; Thacker, 2006). PM2.5 also

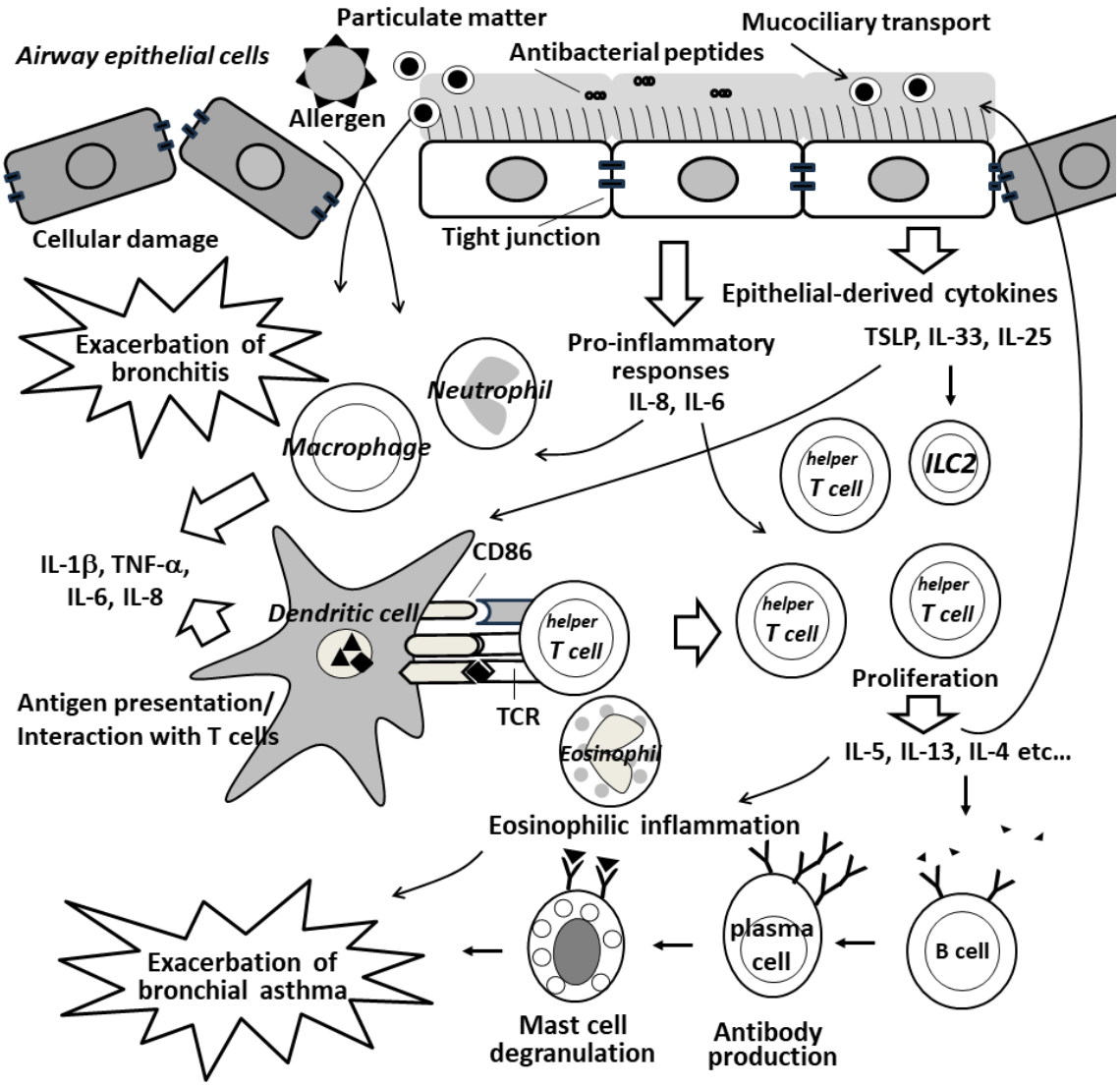

Fig. 1 Effects of particulate matters on respiratory and immune systems.

suppresses the expression of the antibacterial peptides β-defensin2 and β-defensin3 in airway epithelial cells as a factor in increased susceptibility to respiratory infections (Rivas-Santiago *et al*., 2015). Regarding the effects on innate immunity, *in vivo* studies have shown that PM2.5 increases the number of inflammatory cells, especially neutrophils and macrophages, and cytokines, such as IL-6, IL-1β, TNF-α, and KC (an IL-8 homolog) in bronchial lavage fluid (BALF) and lung tissues (Honda *et al*., 2021). These molecules activate acute inflammation (Zhang & An 2007). PM2.5 suppresses macrophage phagocytic activity and nitric oxide production during pneumococcal infection, enhancing pneumococcal infectivity and aggravating pulmonary pathogenesis (Chen *et al*., 2020). In an *in vitro* study, PM2.5 induced IL-6, IL-1β, and TNF-α in bone marrow-derived antigen-presenting cells (Honda *et al*., 2021). Interestingly, the inflammatory response induced by PM2.5 in antigen-presenting cells was drastically suppressed when the particles were removed as an extract (Honda *et al*., 2021); therefore, the shape of xenobiotics is important in triggering an immune response. In addition, the recognition receptors for PM have also been elucidated. SRB-1 and Siglec-14 on antigen-presenting cells recognize silica and multi-walled carbon nanotubes, respectively, leading to the production of inflammatory cytokines, such as IL-1β, and the enhancement of phagocytosis (Tsugita *et al*., 2017; Yamaguchi *et al*., 2023). ILC2 is a new player in the innate immune system and expressed in the lungs, mesentery, skin, etc. ILC2 produces IL-5 and IL-13 in response to epithelial-derived cytokines, such as IL-33, IL-25 and thymic stromal lymphopoietin (TSLP), and induces a Th2-type immune response. IL-5 facilitates eosinophil production and maturation, and IL-13 stimulates epithelial cells to secret mucins (Habib *et al*., 2022). Previous studies have reported that multi-walled carbon nanotubes, O_3, diesel exhaust particles and cigarette smoke activate pulmonary or BALF ILC2 in the presence or absence of allergens (Estrella *et al*., 2019; Lee *et al*., 2019).

Regarding the effect on acquired immunity, in the presence of allergens, PM2.5 has increased the number of

eosinophils, lymphocytes, neutrophils and macrophages in BALF and accelerated eosinophilic inflammation, antibody production and mucus production via IL-5, eotaxin, antigen-specific IgG and IgE, IL-13, muc5AC and TSLP (He *et al*., 2015; He *et al*., 2017; Liu *et al*., 2017: Liu *et al*., 2022). As underlying mechanisms, PM2.5 can activate the TLR2/TLR4/MyD88 signaling pathway (He *et al*., 2017), JAK-STAT6 signaling pathway (Yang *et al*., 2020) and notch signaling pathway (Liu *et al*., 2022). PM2.5-induced airway hyper-responsiveness is involved in the kallikrein-bradykinin pathway (Cao *et al*., 2020), and activation of bromodomain-containing protein 4 (Lu *et al*., 2021) and TRPA1/TRPV1 (Wang *et al*., 2019). In some *in vitro* studies, DEP, PM2.5, or its extracts increased CD86 expression in antigen-presenting cells (Honda *et al*., 2021), antigen-presenting activity for ovalbumin-specific T cell proliferation (Koike and Kobayashi, 2005), TCR expression, splenocyte proliferation (Honda *et al*., 2017) and mast cell degradation (Devouassoux *et al*., 2002). These reactions involving the eosinophils, antigen-presenting cells, T cells and mast cells can act in concert like an orchestra and aggravate allergic inflammation in the lungs.

Studies have also been conducted to narrow down the health-impacting components of PM2.5. Ti and endotoxin/β-glucan were identified by analyzing *in vitro* biological responses and components of PM2.5 collected from Asia with relatively high positive correlations (Onishi *et al*., 2018; Chowdhury *et al*., 2019). Detection of Ti and TiO_2 in the atmosphere from e-waste recycling facilities and high traffic roads has also been reported (Yasar *et al*., 2021; Gallego-Hernández *et al*., 2020). Sagawa *et al*., (2021) revealed that TiO_2 is taken up by alveolar macrophages and that the necroptosis of alveolar macrophages that phagocytose TiO_2 particles is involved in acute lung inflammation. Endotoxins and β-glucans as biological components of PM2.5 can influence exacerbation of asthma (He *et al*., 2017; Zheng *et al*., 2020). Moreover, among polycyclic aromatic hydrocarbons (PAHs), quinone alone or combined exposure to quinones and particles in PM2.5 have induced cell death or reduced viability of airway epithelial cells (Honda *et al*. 2022, 2023). Benzo[a]pyrene disrupts immune response via an increase of CD86 expression on antigen-presenting cells (Chowdhury *et al*., 2007) in addition to being carcinogenic (Moorthy *et al*., 2015). Levoglucosan, mannosan and galactosan are characteristic components of open-burning plants, with a positive correlation with mutagenicity (Van Den Heuvel *et al*., 2018), however, few studies have focused on the relationship between the PM2.5 components of open burning and health effects. Future research should clarify the components that determine the health effects of PM arising from open burning.

2. Effects of PM on COVID-19

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and is a major public health concern on a global scale. Epidemiological studies suggesting a link between COVID-19 and air pollution have been reported from around the world. Specifically, it has been noted that exposure to wildfire smoke may promote COVID-19 morbidity (Centers for Disease Control and Prevention, 2023), and exposure to PM2.5 and PM10 concentrations in the air are positively correlated with the number of COVID-19 cases, the severity of cases and deaths, whether short-term on the order of days or long-term on the order of years (Fattorini and Regoli, 2020; Yao *et al*., 2020; Prinz and Richter, 2022; Shao *et al*., 2022; Xu *et al*., 2022).

There are several explanations for these results, including the theory that SARS-CoV-2 adheres to airborne particles, such as PM, and is transported and diffused that way (Liu *et al*., 2020; Nor *et al*., 2021) and the theory that exposure to ambient PM may also reduce resistance to infection in the population (Maleki *et al*., 2021). However, the exact mechanism is unknown.

Upon SARS-CoV-2 entry into cells, the spike protein (S-protein) on the viral surface binds to the receptor protein angiotensin-converting enzyme 2 (ACE2) expressed on the host cell. Subsequently, the S-protein is degraded through the action of proteolytic enzyme transmembrane protease 2 (TMPRSS2), exposing the fusion active domain within the S-protein, which fuses the viral membrane to the host cell membrane and allows the viral genome to enter the cell (Hoffmann *et al*., 2020; Jackson *et al*., 2022).

Variations in the expression of ACE2 and TMPRSS2 are thought to influence the development of COVID-19 and other diseases (Saheb Sharif-Askari *et al*., 2020), and increased expression of ACE2 and TMPRSS2 in the lungs has been reported in smokers, who have a higher incidence of severe COVID-19 (Chakladar *et al*., 2020). Moreover, smoke exposure increases the expression of ACE2 in the airways in animal models (Yilin *et al*., 2015). This means that the expression of ACE2 and TMPRSS2 varies depending on environmental factors.

Thus, we hypothesized that PM might be involved in the pathogenesis of COVID-19 by affecting the expression of ACE2 and TMPRSS2 and verified this hypothesis in animal studies (Sagawa *et al*., 2021).

Mice from the Male Institute of Cancer Research were intratracheally administered 500 μg of PM particles (PM fine: 0.3 to 2.4 μm particle size, PM coarse: >2.4 μm particle size) collected in Yokohama, Japan, and dispersed in phosphate-buffered saline (PBS). Twenty-four hours later, their lung tissues were collected and immuno-stained for ACE2 and TMPRSS2. The results showed that compared to those in the PBS control group, the number

of cells expressing ACE2 and TMPRSS2 increased in the lung tissues of mice intratracheally administered PM, especially in the alveolar region. Furthermore, multiplex immunostaining, including Mac-3, a marker of macrophages, and proSP-C, a marker of type II alveolar epithelial (AT2) cells, showed an increase in cells co-expressing ACE2 and TMPRSS2 in macrophages and AT2 cells, but especially in AT2 cells.

In human lung tissues, ACE2 and TMPRSS2 are expressed in macrophages and AT2 cells, and these cells are usually the ones that get infected with SARS-CoV-2 (Bertram *et al*. 2012; Adachi *et al*. 2020). In particular, AT2 cells have diverse physiological functions, including the secretion of surfactants, and it is assumed that SARS-CoV-2 infection of these cells causes severe disease.

The results of this study may provide a possible explanation for the association between PM and COVID-19. Elucidating the effects of PM on COVID-19 is crucial for future environmental and hygienic measures, and further research, both epidemiological and experimental, should be developed in this regard.

Acknowledgments

This work was supported by CREST, JST (JPMJCR19H3). We thank Prof. Hirohisa Takano for his supervision.

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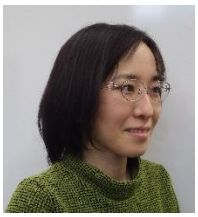

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(Received 30 June 2023, Accepted 28 December 2023)