



The Impact of PM_{2.5} on the Host Defense of Respiratory System

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The harm of fine particulate matter (PM_{2.5}) to public health is the focus of attention around the world. The Global Burden of Disease (GBD) Study 2015 (GBD 2015 Risk Factors Collaborators, 2016) ranked PM_{2.5} as the fifth leading risk factor for death, which caused 4.2 million deaths and 103.1 million disability-adjusted life-years (DALYs) loss, representing 7.6% of total global deaths and 4.2% of global DALYs. Epidemiological studies have confirmed that exposure to PM_{2.5} increases the incidence and mortality of respiratory infections. The host defense dysfunction caused by PM_{2.5} exposure may be the key to the susceptibility of respiratory system infection. Thus, this review aims to assess the impact of PM_{2.5} on the host defense of respiratory system. Firstly, we elaborated the epidemiological evidence that exposure to PM_{2.5} increases the risk of respiratory infections. Secondly, we summarized the experimental evidence that PM_{2.5} exposure increases the susceptibility of different pathogens (including bacteria and viruses) in respiratory system. Furthermore, here we discussed the underlying host defense mechanisms by which PM_{2.5} exposure increases the risk of respiratory infections as well as future perspectives.

Keywords: PM_{2.5}, respiratory system, infection, susceptibility, host defense

INTRODUCTION

Exposure to air pollution, including gaseous pollution and particulate matter (PM) pollution, is a leading contributor to the Global Burden of Disease (GBD 2015 Risk Factors Collaborators, 2016). In recent years, more and more attention has been paid to the impact of PM pollution on public health. PM is a complex mixture of solids and liquids suspended in the air, which can be classified by its aerodynamic diameter as PM₁₀ (<10 μm, inhalable particulate matter), PM_{2.5} (<2.5 μm, fine particulate matter) and PM_{0.1} (<0.1 μm, ultrafine particulate matter). PM originates from natural sources (such as dust, sea salt, and wildfires) and anthropogenic emissions (such as vehicles, household wood and coal burning as well as power plants and industry), and the latter accounts

Abbreviations: AMPs, antimicrobial peptides; AMs, alveolar macrophages; AQLI, Air Quality Life Index; ASL, airway surface liquid; CFUs, colony-forming units; COPD, chronic obstructive pulmonary disease; DALYs, disability-adjusted life-years; GBD, global burden of disease; ICAM-1, intercellular adhesion molecule-1; *K. pneumoniae*, *klebsiella pneumoniae*; *L. monocytogenes*, *Listeria monocytogenes*; LRTI, lower respiratory tract infection; *M. tuberculosis*, *Mycobacterium tuberculosis*; MRSA, Methicillin-resistant *Staphylococcus aureus*; NAC, N-acetylcysteine; NKs, natural killer cells; *P. aeruginosa*, *Pseudomonas aeruginosa*; PM, particulate matter; PM₁₀, inhalable particulate matter; PM_{2.5}, fine particulate matter; PM_{0.1}, ultrafine particulate matter; PMNs, polymorphonuclear granulocytes; ROS, reactive oxygen species; RSV, respiratory syncytial virus; *S. aureus*, *Staphylococcus aureus*; *S. pneumoniae*, *Streptococcus pneumoniae*; SAG, salivary agglutinin; SPD, surfactant protein D; TJs, tight junctions; TLR2, Toll-like receptor 2; TLR4, Toll-like receptor 4; URTI, upper respiratory tract infection; VACES, versatile aerosol concentration enrichment system; WHO, World Health Organization.

for most of the PM pollution (Cho et al., 2018). The components of PM are extremely complex, including inorganic components (such as heavy and transition metals, elemental carbon, and sulfuric/nitric/ammonia salts), organic components (such as polycyclic aromatic hydrocarbons) and biological components (such as fungi, spores, and viruses) (Zhang et al., 2015; Cho et al., 2018). There are certain differences in the source and composition of different types of particulate matter, and the harm to public health varies as well (Figure 1). Among them, PM_{2.5} was considered to be the most harmful one. PM_{2.5} has a large surface area and can adsorb a variety of toxic and harmful substances (Hsu et al., 2016). Because of its small particle size, it can penetrate deep into the lungs and deposit in the terminal bronchioles and alveoli with breath, and even enter the circulatory system through the gas-blood barrier (Pinkerton et al., 2000; Schulze et al., 2017). Exposure to PM_{2.5} can endanger multiple organs in the body, and even lead to systemic adverse effects (Chauhan and Johnston, 2003). Among them, the most common are the respiratory and cardiovascular systems (Xing et al., 2016). This review focuses on the respiratory system, the primary target organ for PM_{2.5} exposure.

PM_{2.5} may be the environmental risk factor that poses the greatest public health hazard. The GBD 2015 ranks PM_{2.5} as the fifth leading risk factor for death, with exposure to PM_{2.5} causing 4.2 million deaths (7.6% of global deaths) and loss of 10.31 million disability-adjusted life-years (DALYs) (4.2% of global DALYs) (Cohen et al., 2017). As claimed by the World Health Organization (WHO), 9 out of every 10 people in urban areas are exposed to high levels of PM_{2.5} (annual average concentration >10 µg/m³) from outdoor air pollution, and about 3 billion people using non-renewable fuels are exposed to serious indoor air pollution (World Health Organization [WHO], 2019). According to the Air Quality Life Index (AQLI), sustained exposure to an additional 10 µg/m³ of PM_{2.5} reduces life expectancy by 0.98 years¹. In addition, an increase of 10 µg/m³ per day of PM_{2.5} concentration increases 0.29% of overall non-accidental mortality and 0.22% of respiratory disease mortalities (Chen et al., 2017).

A large number of epidemiological studies have shown that PM_{2.5} exposure is closely related to a variety of respiratory diseases (Jo et al., 2017; Wang C. et al., 2019). It is noteworthy that exposure to PM_{2.5} increases the susceptibility to respiratory infections. For instance, numerous clinical studies have found that PM_{2.5} exposure is positively correlated with the number of outpatient visits, emergency visits, and hospitalizations for acute upper or lower respiratory infections (Li et al., 2017; Xia et al., 2017; Strosnider et al., 2019). Related animal models also support the notion that PM_{2.5} exposure increases susceptibility to the lung infection (Yang et al., 2001; Sigaud et al., 2007; Zhao et al., 2014). However, the underlying mechanisms remain elusive. We speculate that PM_{2.5} exposure may impair the host defense of the respiratory system, making the body more susceptible to infection. The purpose of this article is to review the existing epidemiological and experimental evidence

to support the above hypothesis and to summarize the possible underlying mechanisms.

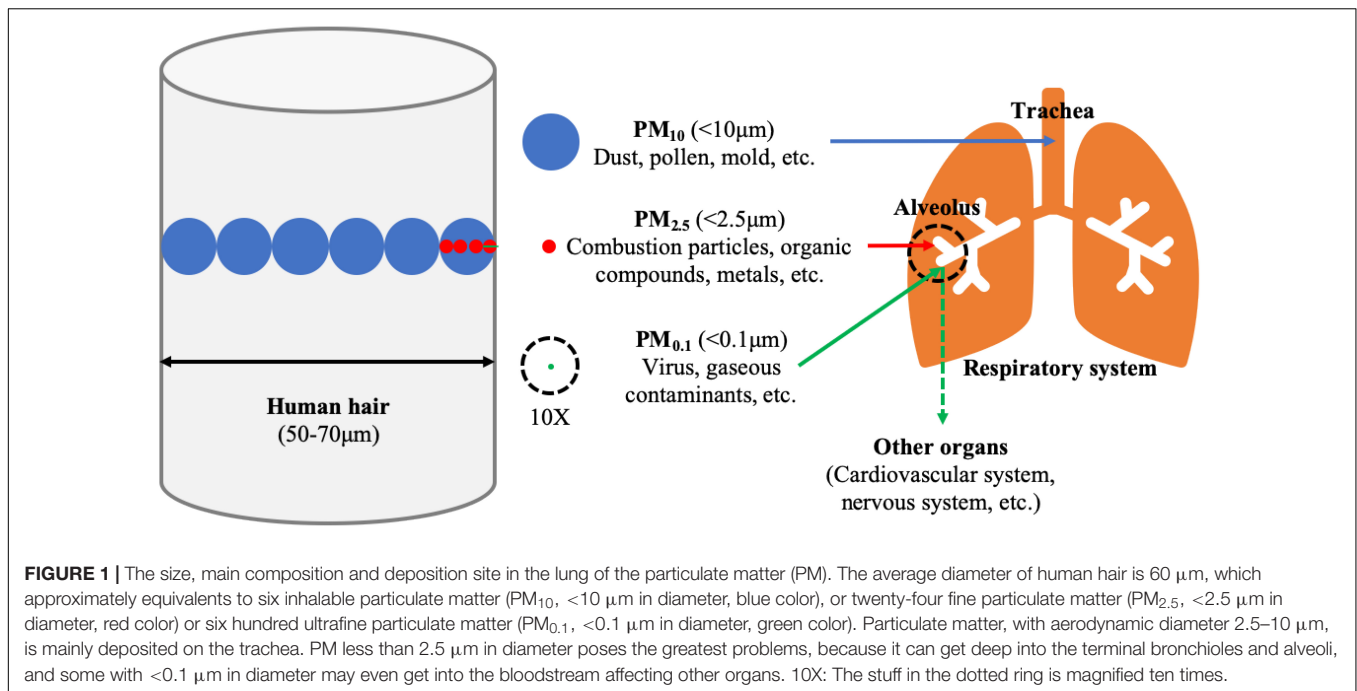
THE EPIDEMIOLOGICAL EVIDENCE

The respiratory system is the primary route for inhaled PM_{2.5}. Exposure to PM_{2.5} can cause the development and progression of acute and chronic lung diseases, such as tracheal and pulmonary inflammation (Kampa and Castanas, 2008; Jedrychowski et al., 2013; Ge et al., 2018), asthma and its acute exacerbations (Habre et al., 2014; Zheng et al., 2015), chronic obstructive pulmonary disease (COPD) and its acute exacerbations (Faustini et al., 2013; Tsai et al., 2013). We are concerned with the fact that PM_{2.5} exposure increases the susceptibility to respiratory infections.

Outpatient, emergency, and hospitalization-related data on respiratory infections confirmed that PM_{2.5} exposure was positively associated with the increased respiratory infections. Li et al. (2017) studied the effects of air pollution on outpatients' acute respiratory outcomes and their study indicated that PM_{2.5} exposure was positively correlated with outpatient visits for upper respiratory tract infection (URTI). A study in the U.S. state of Georgia also showed that pediatric emergency visits for URTI were associated with PM_{2.5} concentrations (Strickland et al., 2016). Another study reported that PM_{2.5} was significantly associated with emergency room visits for respiratory diseases, particularly for URTI and lower respiratory tract infection (LRTI) (Xu et al., 2016). Recently, Strosnider et al. (2019) confirmed that PM_{2.5} exposure was positively correlated with emergency visits for multiple respiratory diseases, including respiratory infections. In addition, Xia et al. (2017) studied the association between different types of air pollution and respiratory hospitalization and found that short-term exposure of PM_{2.5} was positively correlated with the number of hospitalizations for acute respiratory infections. Similarly, another four studies also supported a significant positive correlation between PM_{2.5} and the number of hospitalizations for URTI and LRTI (Belleudi et al., 2010; Li et al., 2018; Liu et al., 2019b; Zhang D. et al., 2019).

The effect of PM_{2.5} exposure on respiratory infections is not immediate, but there is a certain lag effect. For example, PM_{2.5} exposure was positively associated with an increase in hospitalization for acute respiratory infections, but this correlation was delayed by 7–13 days (Xia et al., 2017). Liang et al. (2014) analyzed the time curve of PM_{2.5} concentration and human influenza in Beijing urban area from 2008 to 2011, and proved that there was a significant correlation between PM_{2.5} exposure and influenza, but this correlation showed a 1–2 months delay. In a study of 150,000 cases, Horne et al. (2018) investigated the relationship between PM_{2.5} and the health status of patients with acute LRTI and discovered that the association of PM_{2.5} exposure with respiratory syncytial virus (RSV) infection occurred in 2–4 weeks. The hysteresis effects varied in different studies. Therefore, when investigating the association between PM_{2.5} exposure and respiratory infections, researchers may need to choose the appropriate follow-up time.

¹<https://aqli.epic.uchicago.edu/pollution-facts/?l=en>



Exposure to PM_{2.5} increases the susceptibility to respiratory infections, especially in children and the elderly, as well as the vulnerable groups with hereditary or underlying diseases. A study on the relationship between PM_{2.5} and the health status of patients with acute LRTI revealed that about 77% of the subjects were infants aged 0–2 years. RSV and influenza virus were the main pathogens (Horne et al., 2018). Another study on risks of respiratory infections associated with air pollution in China showed that children under the age of 14 were the predominantly susceptible population of acute respiratory infections caused by air pollution, accounting for 80% of hospitalized cases of respiratory system infections in the study (Xia et al., 2017). Similarly, Liu et al. (2019b) found that students aged 6–17 years were more vulnerable to PM_{2.5} exposure. The maternal exposure to air pollution before birth may result in an impaired lung development and increase the risk of respiratory system infections (Pinkerton and Joad, 2006; Jedrychowski et al., 2013). In addition, by analyzing the association between PM_{2.5} pollution and hospital emergency room visits for total and cause-specific respiratory diseases in urban areas in Beijing, Xu et al. (2016) found that people over 60 years of age demonstrated a higher risk of respiratory disease (including URTI and LRTI) after PM_{2.5} exposure. Exposure to PM_{2.5} is more likely to cause respiratory infections in people with congenital immune deficiencies due to hereditary diseases. For instance, exposure to PM_{2.5} in patients with cystic fibrosis has been reported to be associated with the acquisition of *Pseudomonas aeruginosa* (*P. aeruginosa*). During the follow-up period, each additional PM_{2.5} exposure of 10 μ g/m³ increased the risk of 24% *P. aeruginosa* acquisition (Psoter et al., 2015). Another study has found that each additional PM_{2.5} exposure of 10 μ g/m³ increased the risk

of methicillin-resistant *Staphylococcus aureus* (MRSA) by 68% (Psoter et al., 2017).

THE EXPERIMENTAL EVIDENCE

In vivo studies have shown that as a risk factor for respiratory infection, PM_{2.5} exposure, can prime the lung for greater susceptibility to pathogens by impairing the respiratory host defense. Yang et al. (2001) found that PM exposure suppressed macrophage function and slowed the pulmonary clearance of *Listeria monocytogenes* (*L. monocytogenes*) in rats. Another research discovered that the colony-forming units (CFUs) of *P. aeruginosa* detected in the lung were significantly greater in the PM-exposed mice compared to the control mice (Liu et al., 2019a). Zhao et al. (2014) found that prior PM_{2.5} exposure markedly increased the susceptibility of rats to subsequent *Staphylococcus aureus* (*S. aureus*) infection. Similarly, Duan et al. (2013) found that PM_{2.5} exposure increased the susceptibility of rats to *Klebsiella pneumoniae* (*K. pneumoniae*) infection. Sigaud et al. (2007) and Migliaccio et al. (2013) established an exposure model in mice and subsequently infected with *Streptococcus pneumoniae* (*S. pneumoniae*). They found that PM exposure reduced bacterial clearance in the lungs of mice. In addition, Ma et al. (2017) discovered that exposure to PM_{2.5} lowers influenza virus resistance. We summarized the *in vivo* experimental studies of PM_{2.5} on respiratory host defense (Table 1).

In vitro experiments have also confirmed that PM_{2.5} exposure increased the susceptibility of respiratory infection. For example, PM_{2.5}-pretreated A549 cells have a significantly increased risk of infection with *Mycobacterium tuberculosis* (*M. tuberculosis*) (Rivas-Santiago et al., 2015), and PM can disrupt the airway epithelium through oxidative burst to promote *P. aeruginosa*

TABLE 1 | Summary of *in vivo* experimental studies of PM_{2.5} on respiratory host defense.

Animal species	Pathogen	Exposure method	Effects on respiratory host defense	References
SD rats	Listeria	Intranasal instillation	Exposure to diesel exhaust particles (DEP) decreased the ability of macrophages to produce antimicrobial oxidants in response to Listeria, which may play a role in the increased susceptibility of rats to pulmonary infection	Yang et al., 2001
BALB/c mice	<i>S. pneumoniae</i>	Intranasal instillation	The combination of γ -interferon (IFN- γ) priming and concentrated ambient particles (CAPs) exposure led to an inflamed alveolar milieu where oxidant stress caused loss of antibacterial functions in alveolar macrophages (AMs) and recruited polymorphonuclear granulocytes (PMNs)	Sigaud et al., 2007
BALB/c mice	<i>S. pneumoniae</i>	Whole-body exposure (smoking)	Exposure to wood smoke-derived particulate matter decreased the ability of pulmonary macrophages to effectively mount a defense against infection, and appeared to be mediated via RelB activation	Migliaccio et al., 2013
SD rats	<i>K. pneumoniae</i>	Intranasal instillation	PM _{2.5} exposure increased the susceptibility of the rats to <i>K. pneumoniae</i> infection and decreased bacterial clearance. Its mechanism may be related to the impairment of bronchial mucociliary system and interaction of cytokines.	Duan et al., 2013
Wistar rats	<i>S. aureus</i>	Intranasal instillation	Exposure to PM _{2.5} increased susceptibility to respiratory <i>S. aureus</i> infection in rats via reducing pulmonary natural killer cells and suppressing the phagocytosis ability of AMs.	Zhao et al., 2014
Mice*	Influenza virus	Intranasal inhalation	Long-term exposure to PM _{2.5} lowered influenza virus resistance via down-regulating pulmonary macrophage Kdm6a and mediated histones modification in IL-6 and IFN- β promoter regions	Ma et al., 2017
C57BL/6J mice	<i>P. aeruginosa</i>	Intracheal instillation	PM disrupted tight junctions (TJs) via oxidative stress to promote bacterial infection	Liu et al., 2019a

*The specific strain is not indicated in the literature.

infection (Liu et al., 2019a). Similarly, Chen et al. (2018) found that PM suppressed airway antibacterial defense, causing an increased susceptibility to *P. aeruginosa*. In addition, adhesion is the key to microbial invasion of the respiratory tract. PM increased the binding of *S. pneumoniae* to both primary alveolar macrophages (AMs) and the murine macrophage cell line J774 A.1 but decreased internalization of bacteria (Zhou and Kobzik, 2007). Mushtaq et al. (2011) have discovered that urban PM increased the adhesion of *S. pneumoniae* to human tracheal epithelial cells. We also summarized the *in vitro* experimental studies of PM_{2.5} on respiratory host defense (Table 2).

POSSIBLE MECHANISMS

PM_{2.5} exposure impairs the host defense of respiratory system causing the body more susceptible to infection. We dissect the underlying mechanisms from the following three aspects: defective airway epithelial host defense functions, alterations in respiratory microecology, insufficiency and dysfunction of immune cells (Figure 2).

Defective Airway Epithelial Host Defense Functions

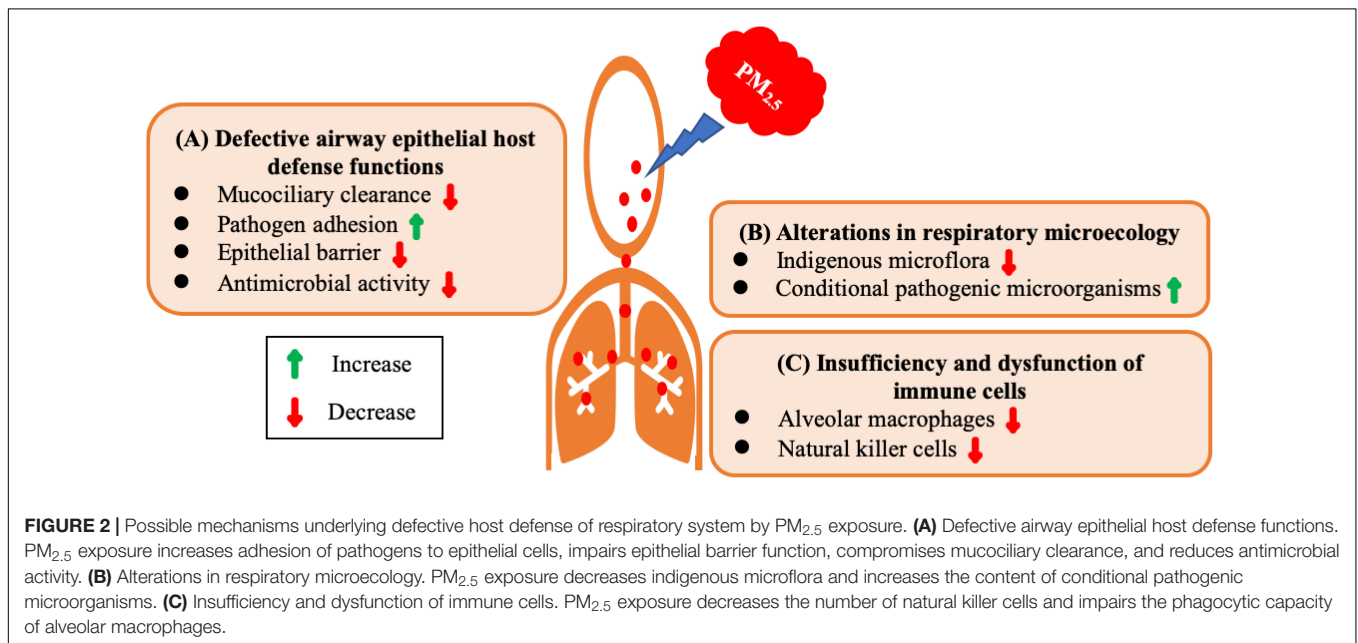
At the interface between the external environment and the host, the airway epithelium serves as the first line of host defense against pathogens. The airway epithelial host defense functions mainly include mucociliary clearance, the barrier functions of the epithelium, and the secretion of a number of proteins and peptides with antimicrobial activities (Figure 3A).

Mucociliary clearance in the airway epithelium is a critical protective function and is essential for the clearance of respiratory pathogens. In general, most foreign bodies inhaled into the lungs can be removed in time by the mucociliary clearance system. However, it has been reported that PM_{2.5} exposure decreased bacterial clearance by impairing the bronchial mucociliary system (Duan et al., 2013). Mucin hyperproduction or hypersecretion is a common reason for decreased mucociliary clearance. Val et al. (2012) found that the expression of MUC5AC, one of the predominant mucins produced by the airway epithelium, was upregulated via the epidermal growth factor receptor (EGFR) pathway after PM_{2.5} exposure in mice (Figure 3B).

The adhesion of pathogens to host cells is a prerequisite for infection. A study has reported that exposure to urban PM increased the adhesion of *S. pneumoniae* to human airway epithelial cells, and the addition of N-acetylcysteine (NAC, an antioxidant) reversed this process, possibly be related to reactive oxygen species (ROS) produced by oxidative stress (Mushtaq et al., 2011). In addition, Liu et al. (2018) reported that ROS induced by PM_{2.5} activated the AKT/STAT3/NF- κ B pathway through IL-6 paracrine signaling, which then upregulated the expression of intercellular adhesion molecule-1 (ICAM-1, an important glycoprotein on the cell surface) in the lung to increase the adhesion of pathogens to the airway epithelium (Figure 3B). Woo et al. (2018) also found that PM_{2.5} could enhance the adhesion of *P. aeruginosa* to epithelial cells, the mechanism of which depended on the increased bacterial surface hydrophobicity and damaged human cell plasma membrane by PM_{2.5}.

TABLE 2 | Summary of *in vitro* experimental studies of PM_{2.5} on respiratory host defense.

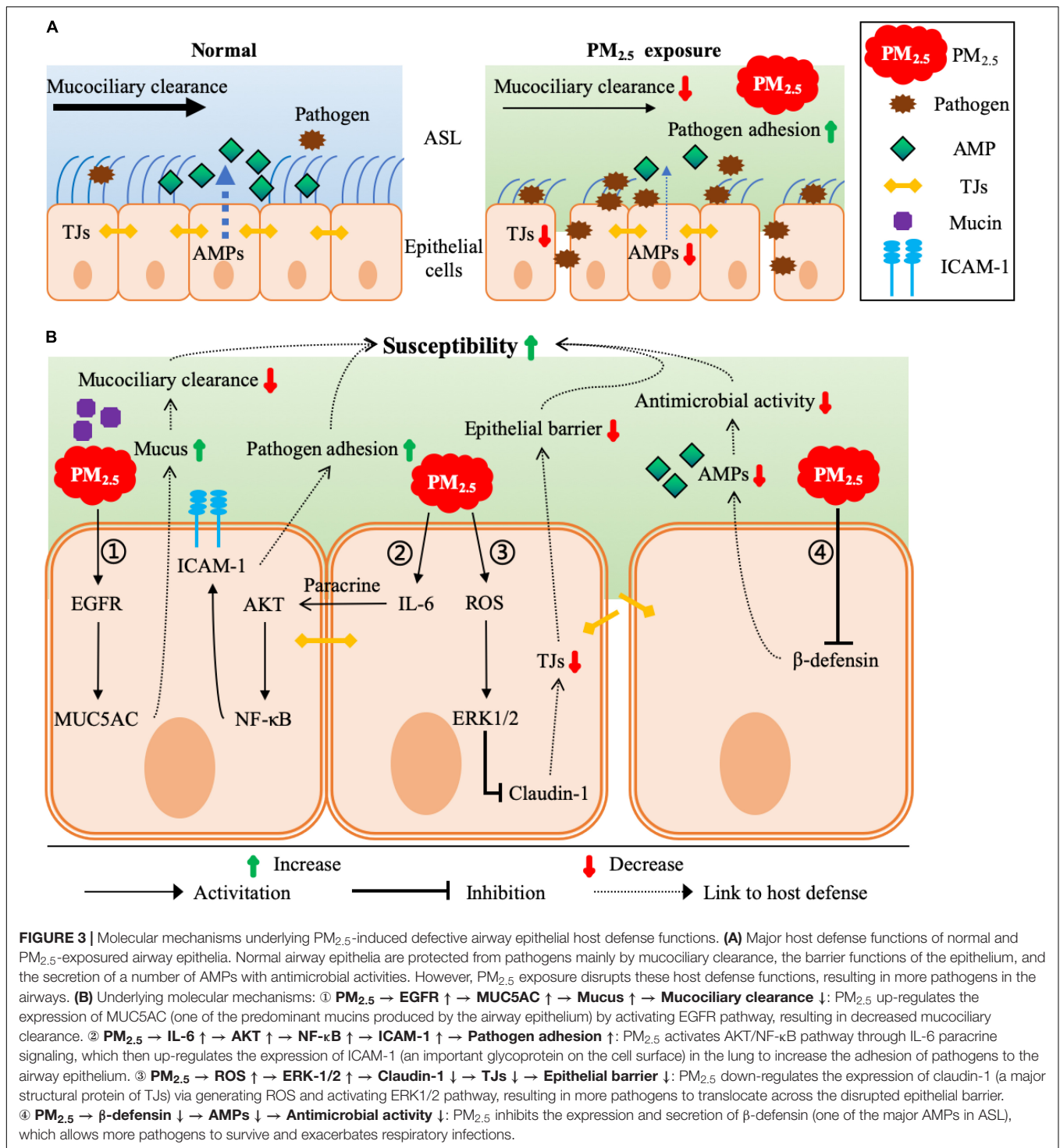
Cell line	Pathogen	Culture method	Effects on respiratory host defense	References
Murine primary alveolar macrophages and the murine macrophage cell line (J774 A.1)	<i>S. pneumoniae</i>	Submerged	Soluble metal, especially iron, in the PM played an important role in the inhibition of macrophage phagocytosis killing of <i>S. pneumoniae</i>	Zhou and Kobzik, 2007
A549 cells and Human primary bronchial epithelial cells (HBEpC)	<i>S. pneumoniae</i>	Submerged	Urban PM increased adhesion of <i>S. pneumoniae</i> to human airway epithelial cells. PM-stimulated adhesion was mediated by oxidative stress and platelet-activating factor receptor (PAFR)	Mushtaq et al., 2011
A549 cells	<i>M. tuberculosis</i>	Submerged	Exposure of A549 cells to PM induced cellular senescence, a likely cause of the observed downregulation of HBD-2 and HBD-3 and the subsequent loss of <i>M. tuberculosis</i> growth control	Rivas-Santiago et al., 2015
BEAS-2B	<i>P. aeruginosa</i>	Submerged	PM impaired airway epithelial defense by impeding the induction of HBD-2 via an oxidative burst, potentially causing an increased susceptibility to infection	Chen et al., 2018
BEAS-2B	<i>P. aeruginosa</i>	Submerged	PM disrupted tight junctions (TJs) via oxidative stress to promote bacterial infection	Liu et al., 2019a



Tight junctions (TJs) are the significant protein complexes at cell-cell interfaces that connect adjacent cells with each other to form lung epithelial barrier against pathogens (Schlingmann et al., 2015). Lack of an intact TJs structure, the airway epithelial barrier cannot keep tight. It will allow pathogens to translocate across the barrier, making the lungs more susceptible to infection. A recent study reported that PM impaired TJs of airway epithelial barrier via oxidative stress to promote *P. aeruginosa* infection (Liu et al., 2019a). Claudin-1 is a major structural protein of TJs. Similarly, another study also discovered that exposure to PM downregulated claudin-1 expression in human airway cells via the ERK1/2 signaling pathway (Kim et al., 2017) (**Figure 3B**).

The airway epithelial cells are covered with a very thin fluid layer (airway surface liquid, ASL), which is an important

component of the respiratory innate immunity. Antimicrobial peptides (AMPs) content is a significant and indispensable factor affecting the antibacterial effect of ASL. AMPs include salivary agglutinin (SAG), beta-defensins, lactoferrin, secretory IgA, and surfactant protein D (SPD) (Fabian et al., 2012; Kendall et al., 2013; Vargas Buonfiglio et al., 2018). Zhang S. et al. (2019) found that PM_{2.5} exposure attenuated the antibacterial activity of airways by down-regulating the expression of SAG. In addition, several studies indicated that PM_{2.5} exposure down-regulated airway β-defensin expression levels through oxidative stress (Rivas-Santiago et al., 2015; Vargas Buonfiglio et al., 2017; Chen et al., 2018). Collectively, these studies suggested that PM_{2.5} could compromise the host defense function of airway epithelial cells by downregulating the expression of AMPs (**Figure 3B**).



Alterations in Respiratory Microecology

In healthy humans, the low respiratory tract is usually sterile, and without permanent bacterial colonization, while the upper respiratory tract (especially oropharynx) has a normal bacterial flora, which is also an important component of respiratory tract's natural immune defense, providing a biological barrier against foreign matter or pathogenic microorganisms through

a space-occupying effect, nutritional competition, and secretion of bacteriostatic or bactericidal substances (Akata et al., 2016; Marsh et al., 2016; Wang L. et al., 2019). The oropharyngeal microecosystems of rats changed following PM exposure, including a decline of indigenous microflora and an increase of the content of conditional pathogenic microorganisms (Xiao et al., 2013). By analyzing 16S rRNA sequencing of respiratory

TABLE 3 | Strengths and weaknesses of intratracheal instillation and versatile aerosol concentration enrichment system (VACES) on PM_{2.5} exposure to experimental rodents.

Method	Intratracheal instillation	Versatile aerosol concentration enrichment system (VACES)	
		Oral-inhalation exposure system	Whole-body exposure system
Equipment cost	Low	High	High
Operation difficulty	High	Low	Low
Animal activity level	Limited	Limited	Unlimited
Dosage	Instilled dosage (mg/kg of body weight or mg/animal)	Defined by the PM _{2.5} concentration (mg/m ³)	
Deposition	Uneven distribution in the lung lobes	Even distribution in the lung lobes	
Application	Acute model, only affecting the lower respiratory tract	Acute or chronic model, affecting the whole respiratory tract	
Source of PM _{2.5}	PM _{2.5} powder is usually obtained through high volume air sampler collection, ultrasonic elution and vacuum freeze drying. Different elution methods have an impact on the composition of PM _{2.5} obtained	PM _{2.5} is collected directly from the air and concentrated for the required exposure concentration. The composition of PM _{2.5} will be affected by the spatial and temporal distribution of the collection sites	

tract lavage fluid, a recent study confirmed that there is a link between PM_{2.5} exposure and alterations of the respiratory tract microecology (Yang et al., 2019).

Insufficiency and Dysfunction of Immune Cells

A variety of immune cells are resident in the respiratory tract, including AMs, polymorphonuclear granulocytes (PMNs), lymphocytes, etc. Their numbers and functions are essential to protect against pathogen invasion. Zhao et al. (2014) found that the reduction of phagocytic phagocytosis caused by PM_{2.5} exposure was related to a decrease of NKs in a PM_{2.5} exposure rat model and subsequently infected with *S. aureus*. Another research found that PM_{2.5} exposure can trigger a Th2-type immune response and reduce the phagocytic capacity of AMs, which may be related to Toll-like receptor 2 (TLR2) and Toll-like receptor 4 (TLR4) (Zhao et al., 2012). In addition, Ma et al. (2017) found that long-term exposure to PM_{2.5} lowered influenza virus resistance via down-regulating pulmonary macrophage Kdm6a and mediated histones modification in IL-6 and IFN- β promoter regions. Another two studies indicated that PM_{2.5} can be used as an immunity inhibitor to reduce the phagocytic capacity of macrophages, thereby increasing the susceptibility to *S. pneumoniae* infection (Migliaccio et al., 2013; Zhao et al., 2014). PM exposure has also been indicated to decrease the ability of macrophages to produce antimicrobial oxidants in response to *L. monocytogenes*, which may play a role in the increased susceptibility of rats to respiratory infection (Yang et al., 2001).

CONCLUSION AND FUTURE PERSPECTIVES

In summary, there are sufficient epidemiological evidences from outpatient, emergency and hospitalization-related data that exposure to PM_{2.5} increases susceptibility to respiratory infections. However, studies on the association between PM_{2.5} exposure and age, gender, and specific pathogens remain controversial. In the future, a meta-analysis of existing research can be attempted to further confirm the susceptible population

of PM_{2.5} exposure to respiratory infections. We notice that there is a lag effect in the association between PM_{2.5} exposure and respiratory infections. This may be due to the variations of the average incubation period of different pathogens. We also note that only a few epidemiological studies have reported the relationship between PM_{2.5} exposure and the infection rates of specific pathogens associated with respiratory infections. Is there a specific pathogen preference for respiratory infections caused by PM_{2.5} exposure? This still requires the unremitting efforts of the researchers.

In vivo and *in vitro* studies have shown that PM_{2.5} exposure is beneficial to the adhesion, colonization and growth of microorganisms, but it is not conducive to the removal from the body. However, most of the current *in vivo* experiments establish a PM_{2.5} exposure animal model by intratracheal instillation. This model usually affects the lower respiratory tract and is prone to uneven distribution in the lung lobes. Concentration and enrichment of PM_{2.5} aerosol combined with the oral-inhalation or whole-body exposure system may be the best model for simulating human exposure. In recent years, an emerging technology has appeared, combing versatile aerosol concentration enrichment system (VACES) with oral-inhalation or whole-body exposure system. The advantages and disadvantages of these two models are shown in Table 3. Furthermore, current *in vitro* experiments are limited to epithelial cells- and alveolar macrophage-mediated innate immune responses, lacking attention to adaptive immune responses. Either *in vivo* or *in vitro*, the exposure doses currently used in the study are usually based on the corresponding toxicity experiments. How can such exposure levels represent real-world or clinical scenarios?

PM_{2.5} exposure may impair the host defense system of respiratory system, making the organism susceptible to infection. In brief, the possible mechanisms include defective airway epithelial host defense functions, alterations of the respiratory tract microecology, and insufficient number or dysfunction of immune cells (Figure 2). However, there is still a lack of robust research on molecular mechanisms. Further efforts are desperately needed to elucidate the underlying mechanisms at the molecular level.

AUTHOR CONTRIBUTIONS

XT conceived and designed the manuscript. LY, CL, and XT wrote the manuscript and critically revised it. CL and XT generated the figures. XT provided guidance and edited the manuscript.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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