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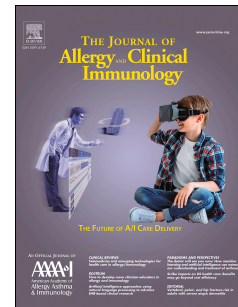
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Air pollution and the respiratory microbiome

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Introduction

Air pollution represents a significant public health concern worldwide. Inhalation of air pollutants such as diesel exhaust induces oxidative stress and inflammation in the airways and is an aggravating factor in chronic respiratory diseases such as asthma, chronic obstructive pulmonary disease (COPD), lung cancer, and recently COVID-19^{1,2}. Despite the critical role of the microbiome in respiratory health, there remains a knowledge gap regarding the impact of air pollution on the respiratory microbiome³.

A healthy adult breathes more than 10,000 L of air a day, containing 10^4 - 10^6 bacterial cells per cubic meter of air. To maintain homeostasis in the respiratory tract (RT) in response to constant environmental stimuli, there exists a complex interplay between the microbiome and immune system³. This homeostasis may be disturbed by environmental pollutants as controlled human exposure studies have revealed that diesel exhaust exposure decreases lung antimicrobial peptides⁴.

This paper advocates for more research to improve the current understanding of air pollution effects on lung microbiome composition and metabolic functions. Moreover, characterizing the ability of the lung microbiota to metabolize pollutants and the resulting metabolites will help manage the overall impact on respiratory health.

Microbiome of the respiratory tract

Culture-independent techniques have enabled the characterization of the lung microbiome, a collection of microorganisms inter-connected with each other and the host, participating in maintaining homeostasis and immune response. The microbiota enhances respiratory defenses to pathogens via granulocyte-macrophage colony-stimulating factor (GM-CSF) signaling, which stimulates pathogen killing and clearance by alveolar macrophages. Increased pulmonary GM-CSF production in response to infection is primed by the microbiome through interleukin-17A⁵.

Alteration of the respiratory microbiome is associated with airway inflammation and chronic lung disease exacerbations. Nevertheless, it is unclear whether or not the alteration of the microbiome is causal or a consequence of the disease. The healthy lung microbiome is dominated by *Firmicutes* and *Bacteroidetes* at the phylum level, and *Prevotella*, *Veillonella*, and

Streptococcus represent the three most dominant genera. Asthma and COPD are characterized by an increase of the *Proteobacteria* phylum, the genera *Haemophilus*, *Moraxella*, and *Streptococcus*, and a decrease of symbiotic bacteria *Prevotella* and *Veillonella*⁶. Exposure to PM increases bacterial invasion of the airway epithelium via oxidative stress, thereby increasing lung bacterial burden and systemic dissemination⁷.

Air pollution, a cocktail of xenobiotics altering the respiratory microbiome

Many studies have focused on the detrimental effects of ambient air pollution, composed of gases (O_3 , NO_2 , CO, and SO_2) and particulate matter (PM), on respiratory symptoms and function¹. Metals such as iron, copper, zinc, magnesium, other transition elements present in PM_{10} (<10 μm in diameter) and $PM_{2.5}$ (<2.5 μm), and associated polyaromatic hydrocarbons increase the production of free radicals and deplete antioxidants, leading to oxidative stress, damage of cellular macromolecules, and release of inflammatory cytokines⁸. Increased reactive oxygen species also results in changes in pH, oxygen availability, and growth conditions within the respiratory mucosa, leading to bacterial injury and death. $PM_{2.5}$, which penetrates deep into the lungs, also disturbs epithelial layer integrity by damaging tight junctions. Consequently, microbes and toxic metabolites can cross the epithelial layer⁷, leading to systemic immune activation and the lung microbiome's alteration (Fig 1).

The microbiome of polluted air

The development of air sampling devices and sensitive microbiome sequencing methods have enabled the characterization of air pollution microbiomes (*eg*, the organisms suspended in air along with, or directly attached to, other PM including that which is combustion-derived) in cities like Beijing⁹. Although otherwise clean air can contain microbial species, analysis of air pollution microbiome during severe smog days showed that the relative abundance of respiratory pathogens in the polluted air is positively correlated with PM concentrations. In particular, Cao et al.⁹ found that bacteria were the most abundant portion of the microbiome reads in samples of $PM_{2.5}$ and PM_{10} , accounting for 86.1% and 80.8%, respectively, followed by eukaryotes (13% and 18.3%), 0.8% archaea, and 0.1% viruses. Mao et al.¹⁰ provided further

evidence that the microbiome associated with polluted air contains live bacteria, including bacteria of the genera *Pseudomonas*, *Moraxella*, *Micrococcus*, *Streptomyces*, and *Bacillus*.

Inhalation of polluted air may therefore plausibly introduce environmental microorganisms in the RT along with toxic gases and particulate matter⁹. Most of the inhaled microbes and particles are cleared from the RT following coughing and mucociliary clearance. However, increased mucus production and impaired mucociliary clearance hampers microbe clearance and increases the risk of infection in patients with chronic airway inflammation.

The association of air pollutants with microbial molecules such as lipopolysaccharide and fungal spores, which are natural ligands for Toll-Like Receptors (TLRs) may increase their immunogenicity by stimulation of TLRs receptors in addition to activating ROS and PAHs sensing pathways⁸.

Microbiome-xenobiotic interaction in the respiratory tract

The human microbiome has been associated with vast metabolic capacity. Although direct evidence of biotransformation of pollutants by the human lung microbiome is missing, lessons learned from the gastrointestinal microbiome indicate the lung microbiota's potential to metabolize inhaled pollutants and suggest that this should be explored. Metabolomics and activity-based protein profiling will be invaluable in identifying microbes with a beneficial metabolic activity that protects against air pollutants. Such knowledge could promote complementary microbiota-oriented strategies to improving respiratory health.

Significance of understanding respiratory microbiome's role in host response to environmental pollutants

Although exposure to air pollutants has been associated with changes in lung metabolites, the interaction between the RT microbiome and pollutants therein has yet to be elucidated. Increased susceptibility to pollutants in patients with lower lung microbiome diversity suggests a possible role for the microbiome in responding to inhaled pollutants via active metabolites. Whether or not biotransformation of pollutants by RT microbiota is beneficial will largely depend on the microbiome composition and metabolic capacities. In the best-case scenario, we expect the healthy lung microbiome to engage in the biotransformation of pollutants to non-

toxic compounds. Further studies are needed to fully understand air pollution effects on the respiratory microbiome's composition and functions, and to identify RT microbes that potentially have a beneficial role in responding to air pollutants. Identification of such microbes could pave the way to interventions that restore and build an effective symbiotic microbial community that protects against the harmful effects of air pollution exposure, especially in people with compromised airways.

Conclusion

Air pollution is a mixture of gases, particulate matter and biological entities which can individually or collectively affect the relatively balanced homeostasis in the RT. The interaction between air pollution and the respiratory microbiome is far from being unidirectional. It is crucial to improve our understanding of these complex interactions between the host, microbiome, and pollutants, and their involvement in respiratory diseases to develop strategies for improving respiratory health.

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Figure legend

Fig 1: Interactions between air pollution and the microbiome in and upon the respiratory tract. Inhalation of polluted air introduces a mixture of gases, particulate matter (PM), polycyclic aromatic hydrocarbons (PAHs), and microorganisms into the respiratory tract. Air pollution exposure induces production of reactive oxygen species that can cause death of the resident microbiota. Air pollution allows associated microorganisms to invade the airway due to a decrease of host defense peptides. Accumulation of reactive oxygen species provokes epithelial layer damage and the crossing of bacteria and toxic metabolites, triggering cytokine production and inflammatory response. Constant inflammatory response will result in microbiome dysbiosis. The red and grey dashed rectangles indicate direct and indirect effect of air pollution on the airway microbiome, respectively. (Abbreviations: AMPs: antimicrobial peptides; TJ: tight junctions; CO: carbon monoxide; NO₂: nitrogen dioxide; O₃: ozone; ROS: reactive oxygen species; SO₂: sulfur dioxide).

