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The Microbiome and Epidemiology

The respiratory microbiome: an underappreciated player in the human response to inhaled pollutants?

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ABSTRACT

Purpose: Microbial communities in or on the body (i.e., the microbiome) are highly physiologically active and influence human health. Although environmental scientists are increasingly aware of the gut microbiome, the respiratory microbiome's role in the human response to inhaled pollutants is largely unknown.
Methods: We reviewed the literature and present mechanisms by which the microbiome might mediate or modify human responses to inhaled pollutants.
Results: The respiratory microbiome has been shown to influence chronic lung disease exacerbations, and increasing evidence indicates a role in disease development. Research also suggests that the respiratory microbiome could plausibly metabolize inhaled pollutants or modulate host inflammatory responses to exposure. Because these responses depend on the microbes present, defining the composition of the resident microbiome and how microbial communities shift with exposure may help to explain variations in susceptibility to inhaled pollutants. Although more research is needed, significant measurement challenges remain for large epidemiologic studies of the respiratory microbiome.
Conclusions: The respiratory microbiome is likely an underexplored intermediate and potential cause of individual susceptibility to inhaled irritants/toxicants. Characterizing the microbiome's role in the human response to inhaled exposures could improve our understanding of the casual agents of exposure and suggest novel public health interventions.

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Inhaled irritants and toxicants represent important environmental exposures that are linked to death and disease. Health effects associated with these exposures include increased risks of lung cancer, heart and respiratory diseases, as well as metabolic disorders [1]. Given continuous exposures across the lifetimes of all people, it is estimated that 3.1 million deaths and 3.1% of disability-adjusted life years are lost globally per year because of exposures to outdoor particulate pollution. Exposures to air pollution from household combustion of solid fuels account for an additional 3.5 million deaths and 4.5% of disability-adjusted life years lost. Active and passive exposures to tobacco smoke further contribute 6.3 million deaths and 6.3% of disability-adjusted life years lost. Collectively, these impacts place the inhalation of air pollutants within the top 10 risk factors for the Global Burden of Disease [2].

Governmental regulations have successfully reduced outdoor air pollution concentrations and limited tobacco smoke exposures in the United States, with corresponding improvements in health [3–6]. Excess risk remains, however, even at levels of pollution below existing standards. In addition, not all individuals bear the same burden of disease from inhaled pollution exposures. Enhanced susceptibility has been reported among children, seniors, and persons with obesity, diabetes, coronary artery disease, and asthma [7,8]. Although these factors may be associated with a several-fold larger risk in any individual investigation, the characteristics conferring risk are not always consistent across studies. This suggests that traditional risk factors may be insufficient to fully identify those at enhanced risk.

In this article we hypothesize that microbial communities, especially those within the respiratory tract, may have an important, yet under-recognized, role in the human response to inhaled irritants/toxicants. Microbes, including bacteria, fungi, and viruses, reside on all human tissues exposed to the external environment. Collectively referred to as the microbiome, microbial communities in or on the body are highly physiologically

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active and known to influence the well-being of their host [9]. While most research is focused on relationships between the microbiome and health, environmental scientists have begun to pay increasing attention to the gut microbiome since microbes of the gut have been shown to metabolize environmental toxicants [10–12], stimulate host inflammatory response, and affect risk of host infection [9]. In spite of the clear physiological parallels, however, very little thought has been given to the role of the respiratory microbiome in the human response to inhaled irritants/toxicants. Here, we describe what is known about the respiratory microbiome, discuss how it and the gut microbiome might influence the human response to inhalation exposures, and encourage researchers to consider the respiratory microbiome as a mechanistic intermediate and potential cause of individual susceptibility to inhaled irritants/toxicants.

What do we know about the respiratory microbiome?

For over 100 years, traditional wisdom was that in those without lung diseases, microbial communities resided only in the upper (i.e., mouth and nose) but not the lower (i.e., lungs) airways. More recently, however, the use of culture-independent, sequence-based techniques has clearly shown that the lungs are not sterile [13,14]. A summary of the current state of the science can be found in several excellent review articles [15–18] with brief highlights in the following paragraphs.

The origins of the microbial communities in the lungs include inspired air, which contains around 100 bacteria/m^3 [19], as well as those microaspirated and/or dispersed from the oropharynx [18,20]. With no physical barrier blocking bidirectional movement, the lungs also actively eliminate microbes via mucociliary clearance, cough, and innate and adaptive host immune responses. In health, alveolar macrophages, antibacterial surfactant, and other environmental conditions (e.g., temperature, pH, and nutrients) inhibit extensive bacterial growth, resulting in low colonization of the lungs as compared to other compartments. For example, it is estimated that there are approximately 1,000 times fewer microbes in the lungs than the mouth and 1 million to 1,000 million times fewer microbes than in the gut [13,21–24]. In spite of their low abundances, there are diverse and dynamic communities present. Bacterial species common to healthy lungs include *Streptococcus, Prevotella,* and *Veillonella* [14,20,22,23].

In diseased lungs, conditions often become more favorable for bacterial reproduction. Evidence of this growth is provided by a small, but growing, literature documenting different bacterial communities between healthy individuals and those with chronic respiratory diseases such as cystic fibrosis, chronic obstructive pulmonary disease (COPD), and asthma [13,14,17,25–28]. For example, individuals with asthma or COPD have been reported to have higher abundances of Proteobacteria than healthy individuals [13,28]. This finding is important because this phylum includes known respiratory pathogens.

Interestingly, it appears as though the respiratory microbiome community structure may not just reflect the presence of a disease but may also correlate with disease severity. For example, differences in bacterial communities in the lungs have been associated with asthma severity [17,25,29,30] and with the frequency of exacerbations in patients with bronchiectasis [31]. There is also evidence that bacterial communities in the lungs are related to responsiveness to therapeutic interventions [27] and administration of probiotics has been shown to reduce the frequency of cystic fibrosis exacerbations [32]. Collectively, these findings suggest an important role for resident bacteria not only in disease development, as proposed by the hygiene hypothesis [33], but also for the initiation of exacerbations and potentially for treatments.

How might the respiratory microbiome influence the human response to inhaled irritants/toxicants?

There is a growing understanding that our microbiota plays a critical role in the development and mediation of many human processes. As some of the first cells in the body encountering inhaled environmental toxicants, it is likely that the respiratory microbiome is both affected by these exposures and affects these exposures (Fig. 1). In the ideal world, the microbiome would serve as a protective shield for human host. However, it is also likely that the human host gets caught in the cross-hairs of the microbial response to inhaled pollutants and experience collateral damage from those interactions.

Inhaled irritants/toxicants deposit throughout the respiratory tract, with larger particles depositing more prominently in the upper airways (i.e., nose) and the smallest particles and gases reaching deep into the lower airways [34]. If these inhaled exposures induce direct oxidative stress or changes to growing conditions such as local alterations in pH, a likely result could be a shift in which microbes are present (i.e., the microbiome community structure). Disrupting the community structure of the microbiome could then result in changes in the functions it performs, with downstream consequences for human health. Specifically, we hypothesize that changes to microbial function will include alterations to the balance of antioxidant and proinflammatory conditions given that the microbiome is known to modulate the host immune response [13,16]. This is important for air pollution exposures since there is strong evidence from controlled and observational studies implicating oxidative stress and inflammation as key mechanisms in the pathogenesis of inhaled pollutants [35]. This conjecture is also consistent with findings that chronic inflammatory conditions such as asthma and diabetes [8,36–41], which themselves have been linked to the

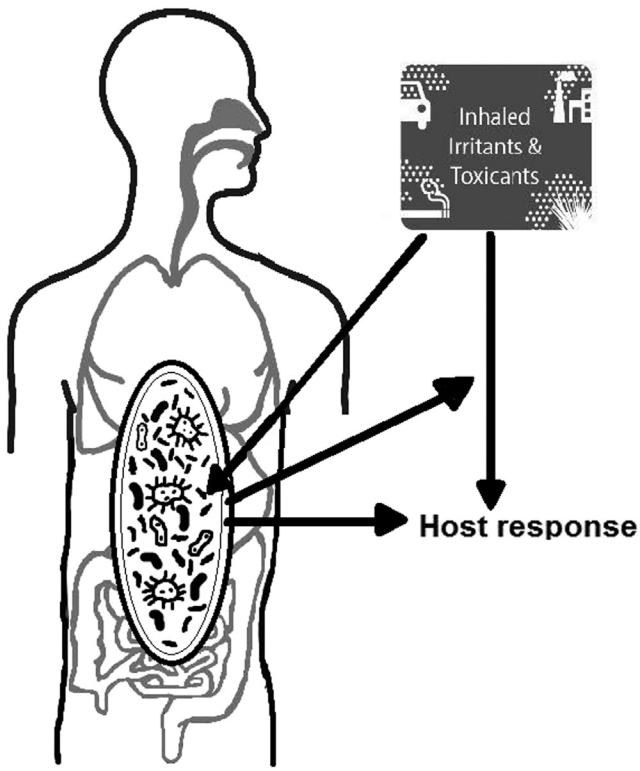

Fig. 1. Hypothesized interplay of inhaled irritants, the respiratory microbiome, and health.

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microbiome, are associated with differential susceptibility to inhaled pollution.

Although there is little known about the impacts of inhaled environmental exposures on the respiratory microbiome, research from the gut has demonstrated selective shifts in microbial community structure and function after the ingestion of environmental pollutants. For example, arsenic-treated mice experienced reductions in Firmicutes but not Bacteroidetes in the gut [42]. These same exposed mice also exhibited bidirectional changes in key metabolites, including those related to bile acids, lipids, amino acids, and isoflavones. Given that many of the observed changes are related to altered absorption of nutrients from the gut, it is plausible that alterations to the microbiome may underlie observed associations between metals and metabolic diseases such as obesity and insulin resistance [43–45]. New evidence also points to changes in the gut microbial community structure after chemical exposures, including reduced bacterial abundance after ingestion of polychlorinated biphenyls by mice [46].

With or without shifts in the microbial communities after exposure, it is also plausible that the microbiome might influence the human response inhaled exposures by transforming chemicals into forms that are more or less bioaccessible to humans. Bacteria have been known for decades to contribute to the biotransformation of environmental metals such as arsenic [47]. Only recently, however, have scientists begun to characterize such biotransformations by the internal microbiome. One seminal study demonstrated that human intestinal bacteria were able *in vitro* to metabolize inorganic arsenic in contaminated soil into methylated arsenic compounds and thioarsenicals [48,49]. More recently, evidence of these transformations has been extended to other pollutants such as polycyclic aromatic hydrocarbons. These typically nonestrogenic by-products of combustion can be converted to compounds with estrogenic-like activity by bacteria from the human colon [10]. Assuming that similar reactions occur within the microbial communities of the respiratory tract, it is likely that the toxicity of inhaled pollutants, which include metals and polycyclic aromatic hydrocarbons, is influenced by microbiome-mediated chemical conversions. In fact, a very recent study demonstrated that administration of antibiotics to mice altered their airway hyper-responsiveness after inhalation of the reactive gas, ozone [50].

Ultimately, because transformations of inhaled pollutants will depend on the specific microbes present and microbial communities differ between individuals [9], it is likely that the microbiome contributes to variations in disease susceptibility. Interestingly, both early lifetime and recent ecological and social settings influence an individual's microbiome [51], suggesting a novel mechanism for adaptation or exaggeration of human responsiveness to long-term exposures.

What evidence is there of a respiratory microbiome response to environmental pollutants?

An extremely small literature on smoking supports the hypothesis that inhaled air irritants/toxicants may impact the respiratory microbiome. Most such research, however, is short term and from the subgingival environment. In this environment, lower abundances of health-promoting microbes and higher abundances of pathogens have been reported with smoking exposures [52]. Interestingly, smoking appears to have a rapid impact on the oral microbiome with changes in bacterial colonization reported within 24 hours [53]. Smoking cessation has similarly been shown to shift the community composition of both dental and intestinal microbes within weeks [52,54].

Chronic differences in the microbiome of smokers have also been suggested in the oropharynx and, to a lesser extent, the nasopharynx [55,56]. By contrast, active smoking has not been shown to alter the community structure of the lower respiratory tract microbiome, at least in individuals with normal lung function defined spirometrically [14,55]. We consider it highly unlikely that the same is true in those with established COPD or asthma of even mild severity, but this is a crucial topic for further investigation.

Finally, epidemiologic studies have shown both cigarette smoke and indoor biomass burning exposures are associated with higher respiratory infection rates from pneumococcal pneumonia, Legionnaire's disease, influenza, and tuberculosis [57–59]. Smoking also clearly depresses the ability to fend off respiratory viral infections [58,60–63]. This in turn may foster the outgrowth of opportunistic respiratory bacterial species that can exploit the niche created by transient epithelial damage induced by respiratory viral infection and the immunosuppression that follows viral clearance [64–66].

What challenges do we face in studying the role of the respiratory microbiome?

One of the key challenges to clinical and epidemiologic research on environmental exposures and the respiratory microbiome relates to existing measurement techniques. Approaches to study microbial communities of the lungs have traditionally included bronchoalveolar lavage and induced sputum [17]. Although previous concerns about the potential for contamination during the bronchoscopic process have been allayed based on results of protected specimen brushing [20,23], both bronchoalveolar lavage and induced sputum are high-burden techniques for healthy individuals. This burden limits the ability of researchers to pursue the large-scale studies likely required to understand the complex interactions that may be at play. For this reason, we and others are actively working to identify a less invasive media that can reliably quantify the respiratory microbiome.

Another important issue for respiratory microbiome research is that of low microbial biomass. Given that microbial communities are present in low abundances in the lungs, extra care must be taken to prevent confusion between the true signal and that from other sources (i.e., "background"). Distortion of the microbial community structure can occur due to the technical aspects of high-throughput sequencing including the presence of nucleic acids from human cells or bacteria in the sampling reagents, differences in extraction protocols, and PCR efficiency [67–70]. Although careful accounting of these sources of noise will produce meaningful results, this is not always the default procedure. Thus, researchers must be diligent in adopting adequate quality assurance protocols for their own research and acknowledging the limitations of findings from laboratories that have not used such procedures.

Finally, we have focused this review on the respiratory microbiome but would be remiss not to acknowledge the potential role of the gut microbiome in the human response to inhaled exposures. First, the theory of a "common mucosal response" implies that lymphoid cells can travel between the gut and lungs to create a widespread inflammatory response [71]. In fact, there is a rich evidence to support the importance of the gut microbiome to the airways with reports of modulation of the immune response to respiratory infection by the gut and associations between the gut microbiome and airway inflammation after allergen or viral challenges [72–75]. There are also direct exposures of the gut to airborne irritants/toxicants as the body clears particles deposited in the lungs to the intestine by way of mucociliary transport [34].

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Moreover, air pollutants can deposit on our food and water supplies [76] with recent evidence that the ingestion of food contaminated by air pollution shifts of the gut microbiome toward increased Firmicutes and Verrucomicrobia and decreased Bacteroidetes [77,78]. Thus, the respiratory microbiome may be only part of the story regarding the role of the microbiome on inhaled pollutants.

Summary and implications

There is a growing understanding that the human responsiveness to external assaults can be shaped by our microbiome. In this article, we presented evidence that the respiratory microbiome is an active player in human health and proposed mechanisms by which the microbiome might plausibly mediate or modify the human health response to inhaled irritants/toxicants. Such a role would have several important implications for our understanding of how inhaled irritants/toxicants impact health and who is most susceptible. First, it would imply new avenues for exploring toxicity and shine a new light on old ones. Characterizing which microbial communities and functions are influenced by or influence exposures may lead to new insights as to which pollutants pose the greatest risk to humans. It may also suggest that added caution may be needed in the interpretation of results from *in vitro* and *in vivo* animal testing when it occurs in the absence of realistic human microbial communities. Second, this line of evidence could provide new insight as to who may be at greatest risk from exposures and suggest novel public health interventions to protect these individuals. For example, the importance of the microbiome to differentiate who is at elevated risk from exposures could open the door for the use of probiotics (live bacteria), prebiotics (to target the growth of certain beneficial bacteria), or targeted antibiotics to shift individuals at heightened susceptibility toward a more protective microbiome. For all these reasons, we encourage investigators to consider the microbiome in future studies of the human response to inhaled irritants/toxicants.

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