Impact of occupational exposure on human microbiota

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Purpose of review
Recent evidence suggests that environmental exposures change the adult human microbiome. Here, we review recent evidence on the impact of the work microbiome and work-related chemical, metal and particulate exposures on the human microbiome.

Recent findings
Prior literature on occupational microbial exposures has focused mainly on the respiratory effects of endotoxin, but a recent study suggests that not all endotoxin is the same; endotoxin from some species is proinflammatory, whereas endotoxin from other species is anti-inflammatory. Work with animals can change the adult human microbiome, likely through colonization. Early studies in military personnel and animal models of gulf war illness show that military exposures change the gut microbiome and increase gut permeability. Heavy metal and particulate matter exposure, which are often elevated in occupational settings, also change the gut microbiome.

Summary
An emerging body of literature shows that work-related exposures can change the human microbiome. The health effects of these changes are currently not well studied. If work exposures lead to disease through alterations in the human microbiome, exposure cessation without addressing changes to the human microbiome may be ineffective for disease prevention and treatment.

Keywords
microbiome, occupational, work, asthma

INTRODUCTION

Why would a person's work environment influence their microbiome, and how does that influence health? Annually in the United States, over half a million cases of occupational illness are reported, costing over 121 billion dollars in lost wages, productivity and medical expenses [1]. Work-related asthma [2] and allergies [3] are common. It is well established that work-related environmental exposures are often orders of magnitude higher than in everyday life, spanning the spectrum of bioaerosols, chemicals, metals and particles. Recent studies suggest both that the microbiome may change in response to toxic exposures and that the microbiome may modulate the effect of these exposures [4]. The purpose of this review is to highlight what we currently know about the influence of occupational exposures on the human microbiome. Research in this field is currently sparse, therefore, we will not solely focus on allergic and inflammatory disease such as asthma. We will distinguish between the effects of biotic and abiotic occupational exposures on the human microbiome.

CAVEATS

Compared to the fields of ecology and marine biology, the study of the microbiome in humans is relatively new and rapidly evolving. In interpreting the literature, it is important to keep a few principles in mind when evaluating studies. First, correlation is not causation. Most early microbiome studies in humans were either cross-sectional (e.g. [5,6]) or did not control for important confounders [7,8] such as medication use (including nonantibiotic medications [9]). These limitations lead to a classic 'chicken or egg' question: Did changes in the microbiome occur because the disease led to changes in

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Curr Opin Allergy Clin Immunol 2019, 19:86–91
DOI:10.1097/ACI.0000000000000502

KEY POINTS

- Recent evidence suggests that work-related microbial and nonmicrobial exposures change the adult human microbiome.
- The health effects of work-related changes to the human microbiome are currently not well understood.
- If work-related exposures lead to disease through changes in the human microbiome, then exposure cessation without addressing the human microbiome may not be enough for disease prevention or treatment.

anatomy or mucosal immunity favoring certain microbes, or do microbiome changes precede and lead to disease development? Randomized controlled trials can address these limitations, but currently no such trials exist in the context of work-related exposures. Animal models are sometimes used to address this issue, but may not approximate the effect size seen in humans.

Second, the sequencing technology used to study the human microbiome, as well as methods and suggested reporting standards for reporting microbiome studies, is changing rapidly. Every step of a microbiome study, from sample handling, storage, DNA extraction and sequencing, can impact the resulting sequencing data generated [10▪]. Furthermore, there may be inadvertent contamination though sample handling or microbial contamination of laboratory reagents used for microbial DNA extraction [11]. There have always been some differences in the bioinformatics pipelines used to analyzed amplification and sequencing of a marker gene such as the 16S rRNA gene, However, in the last 2 years, analysis of such amplicon data has shifted from grouping sequences into operational taxonomic units (OTUs) based on a fixed dissimilarity threshold (usually 3%) to focusing on amplicon sequence variants (ASVs) [12,13] that can differentiate between microbes based on single nucleotide differences at the marker gene. These differences in resolution mean that OTUs and ASVs are not directly comparable.

Finally, while amplicon sequencing of microbial DNA can allow the rapid characterization of which microbes are present ('microbiota'), shotgun metagenomics sequencing, which sequences all microbial DNA and not just marker genes such as the 16S rDNA gene, can identify all microbial genes present, giving the researcher a sense of what metabolic functions the microbial community is capable of ('microbiome'). The Human Microbiome Project has consistently demonstrated that while microbiota may differ between healthy individuals, the functional potential of the microbiome at each body site is conserved [14]. Similarly, in disease, taxonomy does not seem to be as important as function [15]. To date, almost all occupational microbiome studies have focused on amplicon sequencing to resolve taxonomy rather than shotgun metagenomics sequencing to describe function. Furthermore, while current occupational studies have focused on bacteria, viruses and fungi, occasionally archaea (prokaryotes that form a distinct kingdom) are also members of the human microbiome and may play critical roles in health and disease.

THE ROLE OF THE HUMAN MICROBIOME IN HEALTH AND DISEASE

Historically, medical practitioners have focused on microbes as agents of infectious disease [16]. However, as Theodor Rosebury commented in 1969, 'The germ-free animal is, by and large, a miserable creature, seeming at nearly every point to require an artificial substitute for the germs he lacks [17▪▪].' The average person is estimated to have 3.9×10^{13} colonizing microbial cells [18], the vast majority of which are not pathogens but rather important symbionts that serve vital functions [19] such as fermenting starches otherwise indigestible to humans [20], modulating and maturing the immune system [21], providing colonization resistance to pathogens [22] and metabolizing ingested environmental toxins [23]. Shift in entire microbial communities toward a proinflammatory state, termed dysbiosis, has been implicated in diseases we have typically considered noncommunicable. These diseases span almost all organ systems, including obesity [24], diabetes [25], asthma [26,27], inflammatory bowel diseases [28], autism [29] and Parkinson's disease [30]. It is for these reasons that there has been intense interest in how the human microbiome develops, what can perturb it and which factors impact stability.

DOES THE HUMAN MICROBIOME CHANGE AFTER EARLY LIFE?

The human microbiome is the most plastic early in life. At least part of the human microbiome is vertically transmitted from mother to child through vaginal delivery and breastfeeding [31,32]. Some studies suggest that by the age of 3, because of further environmental influences, the toddler's microbiome approaches the adult state [33,34]. It has been postulated that the adult microbiome is largely stable and resilient to change [35–37], but none of these studies have involved the

introduction of new environmental microbiota. A few human studies examining new microbial exposures support the idea that the adult microbiome is plastic. A randomized human experimental study in which healthy adults ingested a specific strain of *Lactobacillus* for 1 week found persistent increases in the presence of this strain in stool 3 weeks after the last exposure [38]. A study of travelers from the United States to either Central America or India showed that healthy travelers as well as travelers who developed traveler's diarrhea (but did not take antibiotics) developed dysbiosis of their gut microbiome [39]. Perhaps the best example is in the use of therapeutic stool transplantation. In *Clostridium difficile* infection, a significant disruption to the gut microbiome exists because of antibiotic use; subsequent stool transplantation allows donor microbes to recolonize the gut. Recolonization because of stool transplantation has also been observed in the absence of preexisting disruptions to the gut microbiome. A recent small placebo-controlled randomized trial of stool transplantation for metabolic syndrome demonstrated that for at least 3 months after stool transplant, individuals had large changes in microbial community structure as well as persistence of donor strains in the gut microbiome; individuals had not used antibiotics or other medications for at least 3 months prior to the transplant [40]. These studies highlight the susceptibility of the adult microbiome to change after the introduction of new environmental microbiota.

OCCUPATIONAL MICROBIAL EXPOSURES AND THE HUMAN MICROBIOME

Although bacteria are ubiquitous in the environment, microbial exposures are elevated in many settings. The highest levels have historically been recorded in work environments [41] such as cotton textile mills [42] and livestock farms [43]. High-level microbial exposures have also been described in schools [44] and cigarette smoke [45,46]. Prior research on occupational microbial exposures has focused on endotoxin as a proxy for microbial exposure. Work-related endotoxin in organic dust has been linked to both asthma and chronic obstructive pulmonary disease [41,47], and is a major determinant of lung function decline [48]. The literature on endotoxin exposure and asthma, however, has been confusing. Although a number of observational studies demonstrate a protective effect of environmental endotoxin exposure on the development of childhood asthma [49,50], others have demonstrated either no effect [51] or even a harmful effect [52,53]; these proneutral-con effects of endotoxin have even been described within the same study [54], adding to the confusion. A recent sequencing study demonstrates that not all endotoxin is the same; endotoxin from some bacterial species is proinflammatory, whereas endotoxin from others is anti-inflammatory. Vatanen *et al.* [55▪▪] showed that endotoxin from *Escherichia coli* elicits a robust cytokine response in human peripheral blood mononuclear cells, whereas endotoxin from *Bacteroides dorei* inhibits the ability of *E. coli* endotoxin to stimulate a cytokine response. This difference led to differential effects of endotoxin exposure on glucose tolerance in a mouse model of diabetes. A recent pediatric asthma study directly comparing toxin vs. nontoxin measures of microbial exposure found no statistically significant association between endotoxin and asthma severity, but an association between exposure to a high diversity of bacteria and increased asthma severity [56]. This and other studies [57▪] show that endotoxin is not a good proxy for environmental microbiota.

Although there is a large body of literature on the microbiome of the built environment [58], few studies have evaluated the influence of indoor microbiome on the host microbiome. There are a few studies in the context of direct human–animal interactions. Home studies show that people share microbes with their pets [59,60]. In the occupational literature, studies show that the upper respiratory tract of livestock workers is colonized by strain-specific methicillin-resistant *Staphylococcus aureus* (MRSA) present in their work environment [61,62]. Work with animals appears to be associated with increased microbial diversity in the nasal microbiome of adult pig and dairy farmers [63,64]; similarly, children living on a farm have higher microbial diversity of their nasal microbiome than their counterparts living in nonfarm rural environments [65]. However, all of these studies were cross-sectional and so temporality and causation cannot be inferred, and furthermore they did not perform analyses directing tracing the nasal microbiome to the environment as a source. A study of poultry abattoir workers found a substantial difference in the gut microbiome of workers over a 5-month period [66], although this study did not evaluate other seasonal exposures as a potential explanatory factor for these temporal changes. Although limited, these studies do support the idea that animal-related work influences the human microbiome.

Does indirect contact with animals in the environment influence the host microbiome? An intriguing study in an agricultural region of North Carolina found that individuals living in census blocks with higher densities of swine also had higher rates of MRSA colonization in their nares; none of

the individuals were livestock workers, precluding direct occupational exposures as the explanation [67]. A recent microbiome study of animal care workers further explored this question. Workers without direct animal contact were tasked with cleaning dirty mouse cages in the cage wash area of animal research facilities [57▪]. Despite low levels of airborne endotoxin, a distinct indoor microbiome was detected in the dirty cage wash area with the most abundant bacteria being those prevalent in the mouse gut microbiome. To determine the proportion of each workers' microbiome that could be directly traced to their work microbiome, each worker was used as their own control and had skin, nasal swab and oral samples collected before and after a standard 8-h shift as well as simultaneous personal air samples for 16S rDNA sequencing. The average proportion of each worker's preshift microbiome attributed to their work microbiome as a source was as follows: $3.1 \pm 1.9\%$ for the nasal microbiome; $3.0 \pm 1.5\%$ for the skin microbiome; $0.1 \pm 0.1\%$ for the oral microbiome. There was a trend toward an increase in the proportion of the nasal and skin microbiome traced to the work environment after 8 h of exposure, though it did not reach statistical significance possibly because of the limited sample size. However, these results suggest that even in a work setting where there is indirect animal exposure, the work microbiome may change the composition of the human nasal and skin microbiome.

One limitation of these studies is that we do not know how these changes in the human microbiome because of the work microbiome impact health. There is some evidence that the work microbiome affects health. School can be viewed as an occupational model for children, given that nearly every child spends the majority of his or her day in school. A recent shotgun metagenomics study of the school environment found that higher classroom microbial diversity was associated with more asthma symptoms [68]. This study did not evaluate whether the mechanism was through alterations in the child's microbiome by the classroom microbiome, or through inhalation of microbial metabolites, but provides some preliminary evidence that the work microbiome can directly impact health.

OCCUPATIONAL NONMICROBIAL EXPOSURES AND THE HUMAN MICROBIOME

There is growing recognition that environmental chemical, metal and particle exposures can change the human microbiome [69]. In the context of work-related chemical exposures, there have been a few studies focused on military personnel who are highly exposed to chemicals including insecticides, insect repellants, sarin and pyridostigmine. A longitudinal study of the respiratory microbiota of healthy military personnel was recently described [70], though this study did not have a control group of nonmilitary personnel to describe whether military exposures were associated with differences in the human microbiome. A mouse model of gulf war illness showed that gulf war chemical exposure leads to dysbiosis of the gut microbiome in decreased gut epithelial barrier function, with resultant portal endotoxemia [71]. These effects appeared to be attenuated with oral administration of butyrate, a short chain fatty acid that is often the byproduct of microbial metabolism [72]. Similarly, there have been studies investigating the effect of pesticide exposures on the human microbiome in farmers. A recent longitudinal study of the organophosphate insecticide azinphos-methyl found that serum concentration of this pesticide was associated with changes in the oral microbiome of farmers. A rat model of chlorpyrifos exposure, a commonly used pesticide, showed that exposure led to significant changes in the gut microbiome and metabolic changes including development of obesity compared to nonexposed rats [73]. A number of microbiome studies have also focused on heavy metal exposure. Arsenic is used by some bacterial as a terminal electron receptor in anaerobic redox reactions [74]. In both human studies and animal models, arsenic at environmentally relevant concentrations alters the gut microbiome [75,76], though it remains unclear how these changes impact human health.

Particulate matter exposure has been strongly linked to lung function, asthma susceptibility and asthma exacerbations. There is an emerging body of literature performed in mouse models demonstrating that exposure to particulate matter alters the composition and metabolic function of the gut microbiome [77,78], and that particulate matter exposure increases gut permeability. These findings have been corroborated in a recent observational study of adolescents, which showed that traffic-related air pollution can alter the gut microbiome [79]. The gut microbiome has been implicated in obstructive lung disease development, and raises the possibility that changes in the gut microbiome may be a novel mechanism by which particulate exposures impact respiratory health [27,80,81].

CONCLUSION

Emerging research shows that work-related microbial and nonmicrobial exposures can change the

human microbiome, although resulting health effects are currently not well defined. If the work environment affects disease development through alterations in the human microbiome, exposure cessation without addressing changes to the human microbiome may be inadequate for disease prevention, control and treatment; this may lead to a paradigm shift in how we approach exposure mitigation to reduce occupational diseases.

Acknowledgements

None.

Financial support and sponsorship

Supported by NIH-NIEHS K23 ES023700 and P30 00002, and a pilot project grant from the Harvard-NIOSH Education and Research Center (T42 OH008416). The funders had no role in study design, data collection and analysis, decision to publish or preparation of the article.

Contributions: P.L. participated in the conceptual design and writing of the article with input from all authors.

Conflicts of interest

There are no conflicts of interest.

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