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# ***Airway Microbiome: Environmental Exposure - Respiratory Health Nexus***

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## **Abstract**

**Toxicants such as smoke, biofuel, and pollutants constantly challenge our respiratory health, but little is known about the pathophysiological processes involved. In a new report, Lin *et al.* provide evidence that our bacterial and fungal lung populations orchestrate the interplay between environmental exposure and lung functions, thereby conditioning health outcomes.**

## **Keywords:**

Airway microbiome; mycobiome ; exposome ; environment ; smoking ; particulate matter

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Human health is continuously challenged by environmental exposures encountered throughout life (also termed “exposome”) [1]. By filtering more than 10,000 liters of air daily, the lung is highly susceptible to this exposome, particularly to toxic compounds or particulate matter (PM) [2]. Long-term exposure of our airways to these toxicants triggers immunological dysregulations promoting various diseases such as asthma, chronic obstructive pulmonary disease (COPD), and cancer [3]. Similar to the gut, the lung hosts broadly diversified communities of microorganisms including bacteria, fungi, protozoa, and viruses. This lung microbiome participates in maintaining the homeostasis of this essential organ and therefore airway health, making the exposome a main perturbator to disrupt the lung microbiome [4]. While it is now well documented that exposure to toxicants impacts lung functions and microbial populations, the exposome-microbiome-respiratory interplay remains poorly understood. In such a perspective, unprecedented insights into the interaction between exposure factors and lung microbial communities with respect to health outcomes were gained through an outstanding report recently published by Lin and colleagues in *Nature Medicine* [5].

By conducting a province-wide, population-based COPD surveillance in China, Lin *et al.* first demonstrated that geography was predominantly associated with the airway microbiome composition. More specifically, their analysis suggested that the distinct districts involved in this study drove the establishment of several types of microbiome profiles including not only bacterial and fungal taxa but also gene functions, antimicrobial resistance genes, and virulence factors. This may indicate that, regardless of the health status of human populations, the microbial communities hosted by the lungs are likely mainly shaped by local exposomes and environmental microfloras. Interestingly, they also found smoking and PM as additional host and environmental factors strongly associated with microbiome profiles highlighting the impact of pollutants on our airway microorganisms. Results also tended to mostly associate smoking with bacterial taxa such as *Atopobium*, *Actinomyces* and *Prevotella*, corroborating with previous studies finding some of these genera in higher abundance in smoker airways [6]. Conversely, their analysis revealed a close association of PM with fungal taxa such as *Cladosporium* and *Penicillium*.

The authors also searched for associations between microbiome features, exposure, lung function, and respiratory symptoms. Some expected positive correlations were primarily found between smoking and PM concentration and loss of lung function. An appealing observation from this study is that most of the microbiome signatures identified tend to mediate the association between lung functions and smoking and PM concentration. More specifically, several bacterial genera were inferred to mediate the association between smoking and lung function while the interplay between PM and respiratory symptoms was found to mainly involve fungal taxa.

Lin and colleagues next tried to identify some interactions between the microbiome and exposure in relation with health outcomes. Among the prominent exposure-outcomes associations revealed, *Neisseria* for bacteria and *Aspergillus* for the fungal counterpart stood out as the main genera interacting with occupational pollution, especially linked to farmland activities, and increased risk for a high respiratory symptom burden. This suggests that people displaying airways with *Neisseria* and *Aspergillus* enrichment could be particularly susceptible to occupational pollution and develop respiratory disorders.

Since the design of their study led to defining healthy airway microbiome signatures and assessing its alteration in diseases, the authors developed a microbiome index indicating respiratory health. For this purpose, they were notably inspired by a recently developed predictive index for health status based on species-level gut microbiome profiling [7]. By

extrapolating to public sputum microbiome datasets, they validated that this “airway microbiome health index” consistently declined in individuals co-experiencing a greater set of exposure factors and respiratory symptoms.

Overall, the new data reported by the research groups of Guan, Zheng, Sun, and Wang obviously represent a major advance in the field of exposology [5]. Indeed, while the investigations carried out in the past years have actively improved our knowledge concerning the composition of the airway microbiome in specific settings of respiratory diseases or exposure, how the airway microbiome underlies the interplay between exposome and respiratory health remained unknown until now. By establishing a “healthy microbiome signature”, they have characterised how the airway microbiome departs from a ‘normal’ state when exposed to pollutants or due to disease.

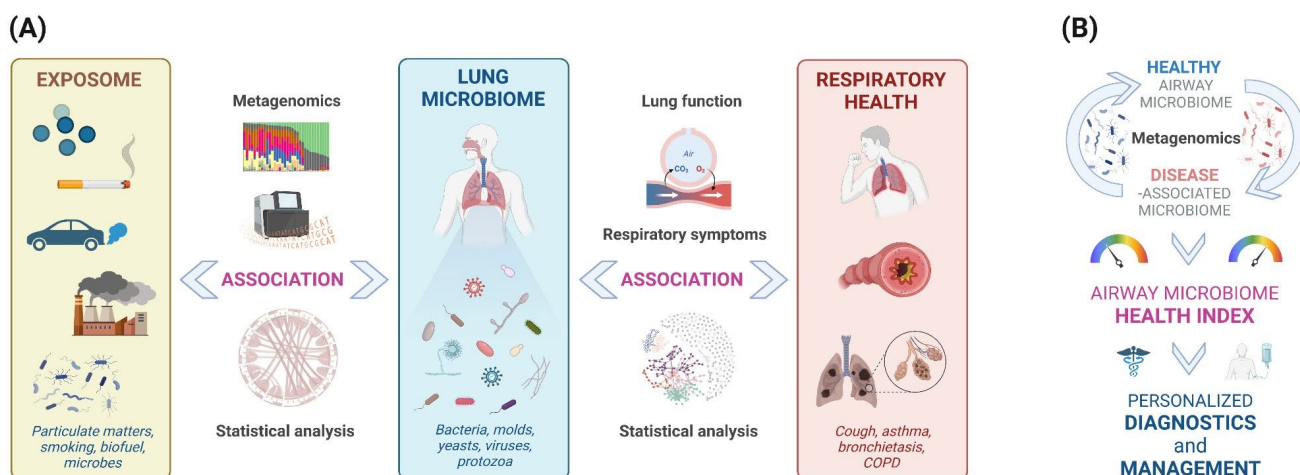
Whilst previous studies have demonstrated the mycobiome is associated with chronic respiratory diseases [8], to date, most of the studies dealing with the lung microbiome focused on bacterial populations, far outnumbering those on the fungal communities. In this regard, it must be admitted that this excellent study focusing on both bacterial and fungal counterparts of the lung microbiome propels new avenues for apprehending an integrated role of fungi in the interaction between toxicants and airway diseases.

Interestingly, all the data compiled in this enlightening article converge toward the unifying evidence that transition from a healthy to a disease status of the airways is conditioned by expansion in inter-kingdom interactions rather than variation in microbial diversity. This study also clarifies that restructuration of bacterial and fungal lung populations is a driving force of airway disease evolution and relies on the modulation of many cell processes such as two component systems, secondary metabolism, drug resistance and virulence suggesting that environmental sensing, stress adaptation, interspecies chemical interactions and pathogenic attributes play pivotal roles in health outcome.

Beyond enriching our understanding of the airway disease pathophysiology, we can anticipate that these discoveries will find applications in personalised diagnostics [9]. Indeed, the individualised microbiome-based health index developed in the study has the potential to be covaried with other factors, such as respiratory disease and smoking, and could be generalisable to other datasets. Individual risk profiles based on the microbiome and additional factors could inform treatment decisions on a personal, patient level - personalised medicine. The presence of specific bacterial and fungal genera/species, coupled with other factors, have the ability to modulate disease and its progression; precision treatment and prognosis promises to develop novel therapeutic action in respiratory medicine. Naturally, the health index could be used as a preventative measure; by assessing the exposome and environmental risk one can guide intervention by offering preventative advice to adjust behaviour and limit exposure. Future microbiome studies should also include fungi, as was done here, and with the development of technologies for fungal detection it is becoming increasingly easier to do so [10]. Finally, with the perspective of diagnostic standardisation, it could be of particular interest to perform in the near future equivalent investigation on different populations/localities for gaining insight into the variation of healthy and disease lung microbiome profiles around the world.

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**Figure 1: Our microbiome mediates the interplay between environmental exposure and respiratory health. (A)** By using metagenomics and statistical analysis, Lin and colleagues initially found environmental exposure associated with microbiome profiles. By searching for associations between microbiome features, exposure, lung function, and respiratory symptoms, they also revealed positive correlations between environmental exposure and loss of lung functions and showed that most of the microbiome signatures identified tend to mediate these associations. **(B)** Lin and colleagues also developed a microbiome index indicating respiratory health. By extrapolating to public sputum microbiome datasets, they validated that this “airway microbiome health index” consistently declined in individuals co-experiencing a greater set of exposure factors and respiratory symptoms. Whilst currently understudied, the host genome could also impact respiratory health e.g. genetic susceptibility to allergies and asthma. Together, this represents of course a step forward toward personalised diagnostics and management.