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The Knowns and Unknowns of Chemically-Induced Lower Respiratory Tract Microbiota Dysbiosis and Lung Disease †

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Abstract: Exposure to chemicals in many occupational and environmental settings have the capacity to significantly disturb the commensual microbiota that symbiotically reside in humans. However, much more is known about gut microbiota (GM) than lung microbiota (LM) due to the challenges of collecting LM samples. The advent of culture-independent methodologies has revealed the complex and dynamic community of microbes harboured by the respiratory tract. It is now being recognized that LM can directly impact immunity in manner that can result in disease. Significant differences in community composition and diversity have been shown between the LM of diseased lungs with those of healthy subjects. Studies have linked LM dysbiosis with human diseases such Idiopathic Pulmonary Fibrosis, lung inflammation, chronic obstructive pulmonary disease (COPD), asthma, lung cancer. However, it is not known whether LM dysbiosis initiates/promotes disease pathogenesis or is merely a biomarker of disease. Many chronic lung diseases often occur together with chronic GIT diseases in what is termed as the gut-lung axis. The LM also affects the CNS, in the bidirectional lung-brain axis, through a number of potential mechanisms that can include direct translocation of micro-organisms. Chemically-induced LM dysbiosis plays a significant part in human diseases as has been shown for air pollution, cigarette smoking and the use of chemical antibiotics.

Keywords: Lung microbiota; dysbiosis; toxicity

1. Introduction

Some human diseases and disorders have been linked to the disturbance/ dysbiosis of the approximately 100 trillion bacteria, fungi, viruses and other microbes that inhabit the human body [1]. In this regard, the human body can be viewed as an ecosystem of distinct habitats of a large diversity and huge numbers of colonizing microbes, with each habitat supporting a discrete collection of microorganisms that interact with each other and with the host. The host-microbiota symbiotic equilibrium is very sensitive to a number of factors, including changes in the concentration of exogenous and endogenous chemicals [2].

For a long time the lung was thought to be sterile and free of microbes [3]. This assertion has recently been disproved, following the advent of culture-independent approaches such as next generation sequencing. The presence or absence of specific microbes in the respiratory tract can have significant effects of the health and well-being of human hosts. For example, the Hygiene Hypothesis suggests that a broad range of microbial exposures contribute to the incidence of allergenic reactions and asthma, both pos-

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itively and negatively [4]. According to the hypothesis, recurrent microbial exposures initiate T-helper 1 (Th1) response rather than a Th2-mediated immune response that is associated with high levels interleukin-4 (IL-4) and IL-5 and eosinophilia [5]. The hypothesis explains the higher prevalence of asthma in urban populations than in rural populations [6]. The Epithelial Barrier Hypothesis also links disrupted epithelia, through bacterial leakage and dysbiosis, with inflammatory diseases such as asthma [5]. The respiratory tract harbours a collection of microbiota that are distinct from those that inhabit the gastrointestinal (GI) tract [7]. Consequently, LM dysbiosis is linked to individual disease conditions are likely to be different from those that result from GM dysbiosis. This study presents the knowns and unknowns of chemically induced LM dysbiosis and disease, especially regarding the microbes that inhabit the respiratory tract, the methods used to analyses LM dysbiosis together with their challenges and recent advances, the diseases linked to LM dysbiosis along with the evidence and the purported mechanisms

2. Respiratory Tract Microbiota and Methodological Issues and Challenges in Its Determination

Because of many limitations such as low culturable bacterial burdens in the lung, contamination during sampling, and challenges in culturing fastidious bacteria, culture-dependent methods could not reveal lung microbial populations. The exponential increase in sequencing technology and bioinformatics analysis have resulted in great insights in lung microbiome in a manner that could not be revealed using culture-dependent methods. Studies using quantitative PCR for 16S ribosomal RNA (rRNA) genes have shown a diverse microbiome often of taxa that are represented in the oral cavity, although lower bacterial burdens have been detected in the lower airways compared to those in the upper airways [3]. Furthermore, the upper respiratory tract microbiota composition in healthy individuals differs significantly from that of the lower respiratory tract. In the lungs of healthy individuals, the predominant phyla are Bacteroidetes and Firmicutes, whereas Firmicutes, Proteobacteria, and Bacteriodetes dominate in the oropharynx [8].

3. Lung Microbiota Dysbiosis and Human Diseases

The structure and diversity of LM vary in different populations (healthy and different diseased individuals) which could play a role in respiratory diseases through a number of mechanisms. As an example, microbiota shape the mucosal immune system as shown by defective immunity in germ-free mice [9]. However, in the respiratory tract little is known about the impact of microbiota on immune cell development and maturation [3]. Nevertheless, children that are exposed to a wide range of microbial exposures, such as those that exist traditional farms, seem to be protected from childhood asthma and atopy. indeed, Ege, Mayer [6] report of lower prevalences of asthma and atopy in children who lived on farms and who were exposed to a greater variety of environmental microorganisms than in children from non-farming environments. The diversity of microbial exposure was inversely related to the risk of asthma, such as exposure to fungal taxon eurotium species, a variety of bacterial species, including Listeria monocytogenes, bacillus species, corynebacterium species, and others, was also inversely related to the risk of asthma. Similarly, Birzele, Depner [10] reported that farming environments were associated with higher bacterial diversity in mattress dust samples as determined by richness and Shannon index, which were in turn inversely associated with asthma.

While the healthy lung is characterized by a prevalence of bacteria belonging to the phyla Bacteroidetes, Actinobacteria, and Firmicutes, asthma (in both young and adults) as well as other viral respiratory infections are associated with abundances of Proteobacteria with genera Haemophilus and Moraxella [7]. Furthermore, many studies have shown that LM dysbiosis can result in a variety of chronic lung disorders such as COPD [11, 12], asthma [13], bronchopulmonary dysplasia (BPD) [14, 15], and cystic fibrosis [16]. However, questions remain on the extent to which chemically-induced LM dysbiosis can

cause or stimulate asthma. In this regard, Li, Sun [17] reported of significant differences in pulmonary function and oropharyngeal microbiota in regions of high, medium and low air pollution.

Cigarette smoking significantly affects the composition of LM. In this regard, Zhang, Chen [18] observed a higher microbial diversity mice exposed to cigarette smoke, while Enterobacter, Acidimicrobiales_norank, and Caulobacteraceae_ were significantly more abundant in the control group. Most importantly, a denser inflammation and congestion were observed in the lungs of the exposed mice than the non-exposed mice. In humans, however, conflicting results have been reported about the effect of smoking on lung microbiota. For example, while Turek, Cox [19] associated smoking with diversity loss, loss of abundance, profound alterations to network structure and expansion of Streptococcus spp. However, Morris, Beck [20] reported similarities between LM of smokers and non-smokers.

Associations have also been made between the use of chemical antibiotics and asthma. Asthma has been reported to be significantly more likely to develop in children who had received antibiotics in the first year of life, with the risk of asthma being highest in children receiving more than four courses of antibiotics [21]. Between 2000 and 2014, Patrick, Sbihi [22] observed a reduction in asthma incidence associated with decreasing antibiotic use in infancy (age <0·0001), whereas in the prospective arm of the study, asthma incidence increased by 24% with each 10% increase in antibiotic prescribing.

3.1. The Gut-Lung Axis

Many chronic lung diseases often occur together with chronic gastro-intestinal tract (GIT) diseases. For example, patients with COPD are two to three times more likely to be diagnosed with inflammatory bowel disease (IBD) [23], while individuals with COPD typically have increased intestinal permeability [24]. Indeed, a number of lung diseases can be influenced by changes in the GI microenvironment, and vice versa, through mechanisms that are still not very clear. A number of mechanism have been postulated: The absorption of signals from the endothelium by epithelial cells and immune cells form a local cytokine microenvironment that leads to changes in distal immune responses. Secondly, short-chain fatty acids (SCFAs) derived from gut bacteria are reported to have inhibitory effects on pro-inflammatory responses in the lungs [25]. Therefore, GM dysbiosis will have effects in the lung and GM dysbiosis early in life has been linked with an enhanced risk for asthma development later in life [7].

3.2. The Lung Brain Axis

The dysbiosis of LM is not only linked to diseases in the lungs and GIT but also diseases in remote parts of the body such as the brain (the central nervous system, CNS). The LM affects the CNS, in the bidirectional interaction known as the lung-brain axis, through a number of potential mechanisms that include direct translocation of micro-organisms, effects of lung microbes on systemic immunity, nerve, HPA axis as well as metabolic changes [26]. The lungs and brain interact through specific signaling pathways or triggered inflammatory factors, largely involving the vagus nerve and the hypothalamic–pituitary–adrenal axis [27]. Furthermore, Hosang, Canals [28] could show a link between LM and brain autoimmunity in rats, where LM dysbiosis significantly affected the susceptibility of rats to developing CNS autoimmune disease. Links between LM and other CNS diseases such as Parkinson's disease, Alzheimer's disease, intracerebral haemorrhage, and glioma are yet to be established. Moreover, Azzoni and Marsland [29] raised a number of questions regarding the role of LM in CNS diseases, including if changes in LM can explain the roles of smoking and respiratory infections in multiple sclerosis, why more patients with chronic lung diseases do not present with neurological disorders, and if LM-derived products can influence CNS.

It is also pertinent know if chemical exposure can induce adverse effects on the CNS via LM-mediated mechanisms. In that regard, intratracheal administration of neomycin was reported to shift the composition of LM to a higher abundance of lipopolysaccharide (LPS)-producing bacteria, which can cross the blood brain barrier to result in the amelioration of autoimmune encephalomyelitis (EAE) [29].

4. Summary and conclusion

The advent of culture-independent methodologies has revealed the complex and dynamic community of microbes harboured by the respiratory tract. LM dysbiosis has been linked with human diseases such Idiopathic Pulmonary Fibrosis, lung inflammation, COPD, asthma, lung cancer. Many chronic lung diseases often occur together with chronic GIT diseases, in what is termed as the gut-lung axis. The LM also affects the CNS, in the bidirectional lung-brain axis, through a number of potential mechanisms that can include direct translocation of micro-organisms. Chemically-induced LM dysbiosis plays a significant part in human diseases as has been shown for air pollution, cigarette smoking and the use of chemical antibiotics.

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