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Microbiota abnormalities in inflammatory airway diseases — Potential for therapy

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ABSTRACT

Increasingly the development of novel therapeutic strategies is taking into consideration the contribution of the intestinal microbiota to health and disease. Dysbiosis of the microbial communities colonizing the human intestinal tract has been described for a variety of chronic diseases, such as inflammatory bowel disease, obesity and asthma. In particular, reduction of several so-called probiotic species including Lactobacilli and Bifidobacteria that are generally considered to be beneficial, as well as an outgrowth of potentially pathogenic bacteria is often reported. Thus a tempting therapeutic approach is to shape the constituents of the microbiota in an attempt to restore the microbial balance towards the growth of 'health-promoting' bacterial species. A twist to this scenario is the recent discovery that the respiratory tract also harbors a microbiota under steady-state conditions. Investigators have shown that the microbial composition of the airway flora is different between healthy lungs and those with chronic lung diseases, such as asthma, chronic obstructive pulmonary disease as well as cystic fibrosis. This is an emerging field, and thus far there is very limited data showing a direct contribution of the airway microbiota to the onset and progression of disease. However, should future studies provide such evidence, the airway microbiota might soon join the intestinal microbiota as a target for therapeutic intervention. In this review, we highlight the major advances that have been made describing the microbiota in chronic lung disease and discuss current and future approaches concerning manipulation of the microbiota for the treatment and prevention of disease.

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1. Introduction

The human body harbors trillions of symbiotic microorganisms covering the intestinal tract, skin, oral cavity as well as the respiratory tract. Referred to as "the human microbiome", it accounts for approximately 1 to 3% of the human body mass. The total number of microbes in the human body exceeds the number of mammalian cells by ten fold (Turnbaugh et al., 2007). The best-studied microbiota is that of the intestine, with 500 to 1000 bacterial species already identified that colonize the mucosal surface of the gut (Human Microbiome Project, 2012). It is well established that there is a very close interaction between the host and its intestinal microbes and that this tight relationship accounts for many beneficial effects. Apart from its basic function in the metabolism of nutritional components (Cummings & Macfarlane, 1997), the intestinal microbiota is also involved in the maturation of the host immune system in a local as well as systemic manner. Several different microbial species such as *Bacteroides fragilis* (Mazmanian et al., 2005; Round & Mazmanian, 2010) and *segmented filamentous bacteria* (Ivanov et al., 2009) are known to affect the balance between inflammatory T helper cell populations and regulatory T cells, and are responsible for the

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induction of inflammatory or tolerogenic conditions. Hence, they are important for establishing as well as disrupting a healthy immune phenotype. Dysbiosis of the interaction between the host and its intestinal microbiota can destroy this steady-state immune balance and can contribute to the development of chronic inflammatory diseases such as inflammatory bowel disease (IBD) (Xavier & Podolsky, 2007). However, not only intestinal disease but also other disorders such as obesity (Tilg & Kaser, 2011) or type 2 diabetes (Larsen et al., 2010) are linked to dysbiosis of the intestinal microbiota, highlighting the importance of an intact microbial community and diversity in the intestine for systemic immune responses.

Although long believed to be sterile, an array of studies in recent years has supported the new concept that the human respiratory tract harbors a local microbiota. Advances in sequencing technologies made it possible to identify the presence of bacterial strains by means of the DNA sequence encoding for specific regions of their 16S rRNA. The majority of these strains cannot be detected by routine culture-based technologies and were therefore missed in early studies addressing this topic. In contrast to the gut, the bacterial load in the healthy lung is at least an order of magnitude lower, however, it comprises of a relatively high diversity of bacterial species. The initial source of the airway microbiota is still unknown, however, there is evidence for a contribution not only of the environment but also of the gut microbiota, as changes in nutrition can impact on the composition of the airway microbiota (Madan et al., 2012). The most prevalent phyla identified in the airways are Proteobacteria, Firmicutes, and Bacteroidetes. Studies at the genus level confirmed the predominant presence of *Pseudomonas*, *Streptococcus*, *Prevotella*, *Fusobacteria*, *Veillonella*, *Haemophilus* as well as *Neisseria* (Hilty et al., 2010; Erb-Downward et al., 2011). Erb-Downward et al. (2011) have shown in a small cohort of COPD patients that the microbiota is different in distinct regions of the airways. However, there is also evidence provided by Charlson et al. (2011) using a two-bronchoscope technique that most of the bacterial species detected in the lower airways reflect cross-contamination from the upper respiratory tract, arguing that a unique lower respiratory tract microbiota does not exist. This remains a key question to be addressed, and advances in sampling techniques and larger scale studies will no doubt provide the basis for a more detailed characterization of the airway microbiota and its distribution in the different compartments of the lung.

2. The airway microbiota in health and disease

Numerous studies of the intestinal microbiota show a strong contribution to homeostatic as well as inflammatory immune responses in the gut (Round & Mazmanian, 2009). So far, there is no direct evidence that the airway microbiota has a similar function in developing and maintaining the steady-state immune phenotype of the lung. However, more and more studies in recent years show an association between the airway microbiota and a variety of chronic lung diseases, indicating changes in the composition of the airway microbiota between healthy and diseased subjects. Even if not yet firmly established, a recent study by Erb-Downward and colleagues suggests the potential existence of a so-called "core airway microbiota", which is similar between healthy people. It is predominantly comprised of *Pseudomonas*, *Streptococcus*, *Prevotella*, *Fusobacterium*, *Haemophilus*, *Veillonella*, and *Porphyromonas* spp. (Erb-Downward et al., 2011). It remains to be seen whether there will be a common consensus between studies, as this "core airway microbiota" might differ between people from distinct ethnical backgrounds and might be dependent on factors such as environmental exposure to microorganisms or diets, as it is the case for the intestinal microbiota. However, the presence of an airway microbiota, and alterations in its constituents dependent on the health status of the individual, are suggestive of a role of the airway microbiota in chronic lung disease.

2.1. Asthma

Several epidemiological studies have shown a clear link between early exposure to microorganisms and the incidence of asthma (Riedler et al., 2001; Ege et al., 2011; Omland et al., 2011), referring to this phenomenon as "the hygiene hypothesis". The increasing use of antibiotic treatment (Droste et al., 2000; Verhulst et al., 2008) as well as the change in lifestyle in westernized countries (Matricardi, 2001), especially including diet (Chatzi et al., 2007; Willers et al., 2011), can lead to alterations in the microbial composition and such conditions

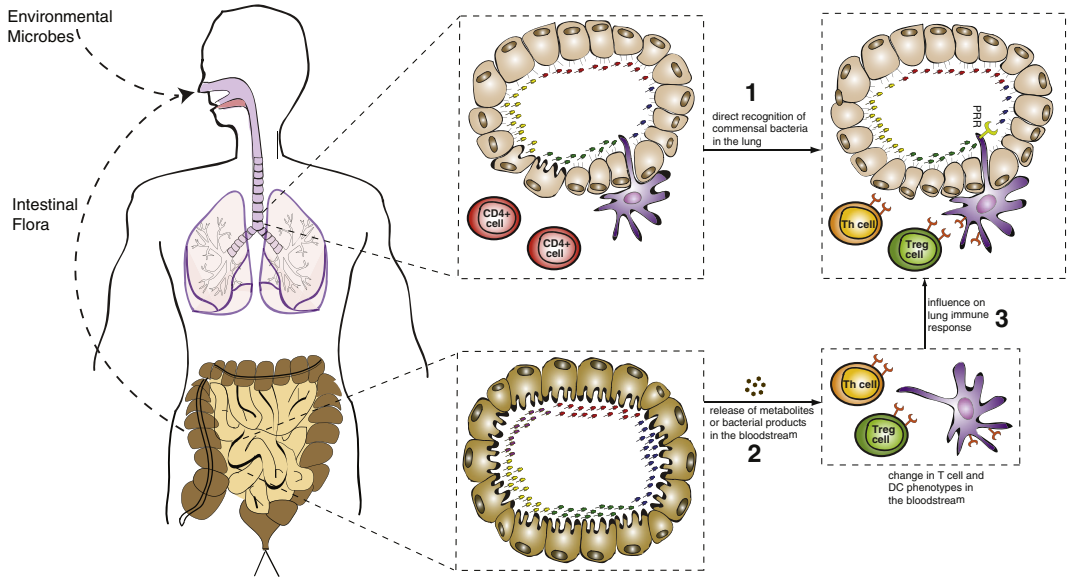

Fig. 1. Shaping of the pulmonary immune response by the commensal microbiota. Although the origins of the airway microbiota are not yet identified, there is evidence that exposure to environmental microbes as well as the endogenous intestinal microbiota might influence the composition of the airway microbiota. The nature of the bacterial constituents could potentially impact on the homeostatic as well as inflammatory immune phenotype in the lung either by (1) direct recognition of the commensal bacteria in the airways by immune cells or (2) via the production of bacterial products and metabolites by intestinal microbes, that are distributed systemically via the bloodstream and (3) influence pulmonary immune responses by systemically altering DC and T cell phenotypes.