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REVIEW

New developments providing mechanistic insight into the impact of the microbiota on allergic disease

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Abstract The increase in allergic diseases over the past several decades is correlated with changes in the composition and diversity of the intestinal microbiota. Microbial-derived signals are critical for instructing the developing immune system and conversely, immune regulation can impact the microbiota. Perturbations in the microbiota composition may be especially important during early-life when the immune system is still developing, resulting in a critical window of opportunity for instructing the immune system. This review highlights recent studies investigating the role of the microbiome in susceptibility or development of allergic diseases with a focus on animal models that provide insight into the mechanisms and pathways involved. Identification of a causal link between reduced microbial diversity or altered microbial composition and increased susceptibility to immune-mediated diseases will hopefully pave the way for better preventive therapies.

Contents

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1. Introduction

The intestinal microbiota is the major component of the host-microbial superorganism when one considers the number of cells, genes and metabolic capacity that it contributes to the superorganism. Although the density and complexity of the microbiota are highest in the lower intestine, all mucosal surfaces, such as the skin, the oral cavity and the lung, harbor a resident microbiota. The microbiota of each body site has its own microbial profile and diversity index.

Many studies have linked disturbances (or dysbiosis) of the microbiota to the development or progression of diseases. Diseases that appear to be impacted by alterations in the microbiota or linked to dysbiosis include metabolic diseases, autoimmunity, inflammatory diseases, neurological diseases, and allergy (reviewed in [1]). Of note, studies linking the microbiome to allergic diseases have increased over the past years and new data supporting a causal link between low diversity microbiota and development of allergy is emerging. Already in the late eighties the British physician David Strachan proposed what is now referred to as the 'hygiene-hypothesis' [2]. Since then a steady increase in the occurrence of asthmatic and allergic diseases, such as food allergy, has been reported in industrialized countries [3]. Several environmental factors have been implicated, including decreased exposure to commensal microbes and infections, wide usage of antibiotics, water decontamination, a continuous cold-chain delivery and food pasteurization, all of which have become standard in developed countries.

The evidence for the dependence of disease development and changes in the microbiota is often deduced from clinical correlative studies in the human population. One approach of such studies is to monitor the intestinal microbial composition during active disease and/or during periods of remission and then evaluate whether active disease could be the cause or consequence of changes in microbial composition, or conversely, whether changes in the microbiota pave the way for disease development or relapse. Other studies analyze the composition of the intestinal microbiota following birth and throughout infancy and retrospectively drawing conclusions from allergy or asthma development during childhood. These studies have provided evidence that allergic diseases correlate with changes in the microbiota [4–8]. However, it is difficult to gain mechanistic insight into how bacteria can shape an allergic immune response from correlative studies. In this review we will summarize recent publications that analyze mechanisms and pathways that play a role in allergic or asthmatic diseases. We will describe what is known regarding development of the microbiota after birth and illustrate recent studies that have started to provide mechanistic understanding into how the microbiota impacts on development of allergic diseases. We provide evidence for a critical window of microbiota development that marks a crucial time in which we can profit from adequate microbial-mediated immune stimulation and highlight new studies investigating the role of the lung microbiome.

2. Intestinal microbiota

During the first three years of life our intestinal microbiota establishes an adult-like microbial community that we largely maintain for the rest of our lives [9,10]. After birth the newborn intestine is an aerobic environment that allows inhabitation of facultative anaerobes like Enterobacteriaceae. Within a few days the lumen becomes anaerobic, thus allowing other obligate anaerobic species, for example Bifidobacteria, *Clostridium* spp. and Bacteroidetes, to populate the intestine. It is now accepted that this initial colonization is heavily influenced by the mode of delivery [11]. The microbiota of children born with cesarean section (resembling the skin microbiota) largely differs from children born vaginally (vaginal microbiota) [11]. Delivery via cesarean section correlates with delayed colonization with Bacteroidetes, a lower abundance of Bifidobacteria and Bacteroidetes, and an overall lower bacterial complexity even at one year of age [12]. Correlation studies suggest that cesarean-born children are more likely to develop obesity [13] inflammatory bowel disease (IBD) [14], or asthma or atopic diseases [15] (critically reviewed in [16]) before adulthood. During the first month of life breast or formula feeding also impacts composition of the human gut microbiota [17]. The introduction of solid food then leads to drastic shifts in composition and complexity of the intestinal microbiota. The presence of new substrates in the intestine, such as non-digestible carbohydrates, causes a shift of the microbial community to incorporate those species that can utilize and survive on the available energy sources. For example, relative proportions of Bifidobacteria or Enterobacteria decrease while relative proportions of some Clostridia species increase their relative abundance [18]. With these changes microbial composition and diversity become more 'adult-like', and also more stable (Fig. 1). The adult microbiota is represented by two main phyla: Firmicutes and Bacteroidetes. Firmicutes comprise mainly the genera *Clostridium*, *Faecalibacterium*, *Blautia*, *Ruminococcus*, and *Lactobacillus* while Bacteroidetes are mainly represented by *Bacteroides* and *Prevotella*. Less abundant are other phyla such as Actinobacteria (Bifidobacteria) or Proteobacteria (Enterobacteriaceae).

Although the gut microbiota is relatively stable in healthy adults, it is influenced by a variety of environmental factors, such as antibiotic use and the diet. It is probably not surprising that the food we consume and the relative amounts of fat, fiber or sugar play a profound role in shaping our microbiome and thereby influencing our immune system. The interplay between diet, microbiota, and the immune system is illustrated in Fig. 2. Dietary metabolites are small molecules that are derived from the food. They can be divided into microbiota-independent metabolites, such as aryl-hydrocarbon receptor ligands, retinoid acid, or folic acid or microbiota-dependent metabolites such as short-chain fatty acids (SCFAs), vitamin K or bile acids. The receptors for dietary or bacterial metabolites are widely expressed in our immune system and are particularly abundant on innate cells like macrophages or innate lymphoid cells. The interplay between the diet, metabolites and inflammation has been the subject of a recent comprehensive review [19] and therefore will not be discussed in detail here.

Recently, it was proposed to classify every human microbiome into one of three "enterotypes" [20] but until now no agreement on a "normal" or healthy microbiota has been made. Currently the ratio between the Firmicutes and Bacteroides abundances and the overall diversity of the microbiota seem to be most predictive of any correlation of the microbiome with a variety of diseases and is widely used as a read-out.