Gut matters: Microbe-host interactions in allergic diseases

Gabriele Hörmannsperger, PhD,* Thomas Clavel, PhD,* and Dirk Haller, PhD *Freising-Weihenstephan, Germany*

The human body can be considered a metaorganism made up of its own eukaryotic cells and trillions of microbes that colonize superficial body sites, such as the skin, airways, and gastrointestinal tract. The coevolution of host and microbes brought about a variety of molecular mechanisms, which ensure a peaceful relationship. The mammalian barrier and immune functions warrant simultaneous protection of the host against deleterious infections, as well as tolerance toward harmless commensals. Because these pivotal host functions evolved under high microbial pressure, they obviously depend on a complex network of microbe-host interactions. The rapid spread of immune-mediated disorders, such as autoimmune diseases, inflammatory bowel diseases, and allergies, in westernized countries is thus thought to be due to environmentally mediated disturbances of this microbe-host interaction network. The aim of the present review is to highlight the importance of the intestinal microbiota in shaping host immune mechanisms, with particular emphasis on allergic diseases and possible intervention strategies. (J Allergy Clin Immunol 2012;129:1452-9.)

Key words: *Intestinal microbiota, bacteria, barrier function, allergy, asthma, eczema, immune responses, oral tolerance, functional food, probiotic*

Abbreviations used
DC: Dendritic cell
MAMP: Microbe-associated molecular pattern
MLN: Mesenteric lymph node
PP: Peyer patch
SCFA: Short-chain fatty acid
Treg: Regulatory T

Allergies, including asthma, dermatitis, rhinitis, and food allergies, are chronic inflammatory diseases driven by deregulated immune responses toward minute amounts of harmless antigens (allergens). Epidemiologic and clinical studies indicate that the increased incidence of autoimmune and allergic diseases in developed countries is associated with reduced microbial exposure and alteration of microbial communities in various body sites.[1] Recent advances in high-throughput molecular technologies in the field of metagenomic and metabolomic analysis have opened up new ways to identify core microbial communities linked to the onset of pathologies.[2-5] Nevertheless, it is still challenging to reach consensus in the definition of a "normal healthy" microbiota of the human gut, airway, and skin at the functional level. Moreover, the molecular mechanisms underlying microbe-host interactions that shape host immune functions are still elusive. In the present review we intend to discuss up-to-date knowledge of how the host microbiota is involved in the regulation of immune responses and the development of allergic disorders. We will provide a brief summary of clinically relevant evidence of the role of microorganisms in allergies, highlight the central role of the gut and its microbiota in regulating peripheral immune functions, and finally discuss data on the use of prebiotics and probiotics for the treatment or prevention of allergic symptoms.

IMPORTANCE OF MICROBE-HOST INTERACTIONS FOR ALLERGIC DISEASES: EVIDENCE FROM HUMAN STUDIES

Our gut harbors the majority of mammalian-associated microbes (10^8 to 10^{12} colony-forming units/g intestinal content). The intestinal microbiota, which is defined as the highly complex and dynamic assemblage of the thousands of microorganisms living in our gut,[5] has therefore been proposed as a major non–self-factor affecting the development of allergies. Changes in gut microbial composition have been reported in patients with allergic diseases at distant body sites, such as rhinitis and atopic eczema.[6-9] Alterations of the intestinal microbiota might actually precede the development of allergic manifestations in children, supporting the hypothesis that microbial dysbiosis is not only a consequence but also a cause of allergy.[10,11] Beyond the gut, the microbiota of the skin and bronchi was also altered in patients with allergic diseases at the respective sites (eczema or asthma).[12-15]

Potential reasons for microbial dysbiosis in allergic subjects lie in complex individual-specific interactions between genetic predispositions[16] and environmental factors, such as birth delivery mode, diet, hygiene, and medication. Birth delivery mode, for instance, markedly influences initial microbial colonization of newborns.[17,18] Natural birth, which results in immediate exposure of the child to the mother's vaginal and fecal microbiota, is associated with a reduced incidence of allergies compared with that seen in children born by means of cesarean section.[19] The revised hygiene hypothesis states that reduced microbial exposure in early childhood results in an increased T_H2/T_H1 response ratio and in defective regulatory immune mechanisms that contribute to a

From Biofunctionality, ZIEL–Research Center for Nutrition and Food Science, CDD Center for Diet and Disease, Technische Universität München.
*These authors contributed equally to this work.
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Corresponding author: Dirk Haller, PhD, ZIEL–Research Center for Nutrition and Food Science, Technische Universität München, Gregor-Mendel-Str 2, 85350 Freising-Weihenstephan, Germany. E-mail: haller@wzw.tum.de.
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higher incidence of immune-mediated diseases, such as allergies, in developed countries.[20] In line with the hygiene hypothesis, growing up in a farming environment, including close contact with cows and consumption of raw milk, is strongly associated with reduced incidence of allergic diseases.[21] Although the farming environment seems to be protective through exposure to increased numbers and varieties of microorganisms,[22] its effect on the intestinal and bronchial microbiota, as well as potentially protective microbes, remain to be characterized. Exposure to pathogens, such as *Helicobacter pylori*, parasites, or *Mycoplasma tuberculosis*, have also been associated with reduced incidence of allergic diseases.[23-25] However, protective effects are pathogen specific, and early viral infections of the airways are a risk factor for allergic asthma.[26] Finally, breast-feeding and the use of antibiotics are 2 additional factors that markedly influence the intestinal and extraintestinal microbiota.[27-31] However, clinical results concerning their effect on allergy development are still conflicting.[32-35]

In summary, clinical data strongly suggest that microbial inhabitants of the human body, especially the intestinal microbiota, influence the development and severity of allergic diseases. Characterization of microbiota dysbiosis beyond phylogenetic diversity analysis is now essential to identify alterations of core microbial functions that contribute to early immune disturbances in allergic patients.

THE INTESTINE AS GATEKEEPER OF IMMUNITY

The intestine emerged as an important target in the prevention and therapy of allergies because the intestinal immune system has unique regulatory functions that affect local and systemic immune responses.[36] In the following paragraphs, we focus on 2 intestinal functions of relevance for systemic immune reactions: gut barrier and oral tolerance.

The intestinal mucosa provides the border between inner tissues and tremendous amounts of mostly harmless food- and bacteria-derived antigens. It is usually very efficient in preventing translocation of microorganisms and reducing the amount of permeating microbe-associated molecular patterns (MAMPs) and antigens.[37] However, increased gut permeability in pediatric and adult patients with asthma and eczema was reported in several clinical and *ex vivo* studies.[38-41] Both acute and chronic barrier disruption caused by mechanical damage, infection, dysbiosis (eg, resulting in overexpression of bacterial proteases), or dietary components can enhance translocation of microbial triggers that can act in distant body sites, such as the lung or skin.[42-44] For instance, diet-induced barrier alterations can result in increased occurrence of LPSs in the blood, which was in turn found to promote the development of diabetes.[43,45] Recent studies in mice provided additional evidence linking gut barrier function to inflammatory responses in distant body sites.[46,47] The authors demonstrated that intestinal epithelial barrier breakdown (eg, enhanced translocation of fluorescein isothiocyanate–dextran and reduced occludin protein levels) contributes to acute lung inflammation after skin burn. By means of surgery (abdominal vagotomy and stimulation of the right cervical nerve), they concluded that the neuroenteric axis is essential for gut barrier–mediated prevention of secondary acute lung injury. All these findings indicate that gut permeability is a promising function worth further investigation in the context of allergy development.

Because inflammatory immune responses toward low levels of penetrating MAMPs and antigens would be detrimental to the host, the intestinal immune system evolved to be highly tolerant toward these structures. An array of innate and adaptive tolerance mechanisms ensures prevention of inflammatory reactions toward harmless MAMPs and antigens.[48] Anti-inflammatory microenvironments in the intestinal mucosa, the gut-associated lymphoid tissue, and the mesenteric lymph nodes (MLNs) favor the development of IgA-secreting B cells and antigen-specific regulatory T (Treg) cells, 2 major antigen-specific tolerance mechanisms.[36] In contrast to other immunoglobulin-driven reactions, antigen binding by IgA results in efficient antigen neutralization without induction of proinflammatory signaling cascades. In addition, the export of high amounts of dimeric IgA toward the intestinal lumen through intestinal epithelial cells results in efficient immune exclusion of the respective antigen and reinforces the intestinal barrier.[49] Low levels of fecal IgA have been associated with increased development of IgE-mediated allergic diseases in children, supporting the relevance of IgA for systemic immune homeostasis.[50] Importantly, the induction of antigen-specific Treg cells on oral antigen exposure not only confers gastrointestinal but also peripheral tolerance toward the specific antigen (oral tolerance, Fig 1). Antigen-specific Treg cells exert potent anti-inflammatory activities, either through suppression of cell-cell contacts or secretion of anti-inflammatory cytokines, such as IL-10 and TGF-β.[51] Noticeably, the capacity to induce tolerogenic mechanisms toward antigens can also be referred to as mucosal tolerance because it is not exclusive to the gastrointestinal tract but rather a general feature of mucosal body surfaces, including nasal and bronchial mucosa.

The induction of mucosal tolerance is an important and extensively investigated therapeutic goal in patients with a wide range of chronic inflammatory diseases.[52-55] In the context of allergies, sublingual immunotherapies have been successfully developed to reduce systemic reactivity toward the respective allergen through induction of oral tolerance.[56] However, deregulated intestinal immune responses, such as those in patients with food allergies, in which the immune system is overreacting toward minute amounts of food antigens, or inflammatory bowel diseases, in which an overreaction toward microbial antigens triggers chronic inflammation, were found to be associated with strongly reduced or loss of oral tolerance.[57,58] These findings indicate that oral tolerance is dependent on the proper development and function of the intestinal barrier and immune system, which in turn are shaped by microbe-host interactions. In the next section we will provide details on the role of microbe-host interactions in the development of specific immune cell populations and immune mechanisms that are thought to underlie the development of allergies.

EFFECT OF MICROBE-HOST INTERACTIONS ON INTESTINAL AND SYSTEMIC IMMUNE FUNCTIONS

The major role of microbe-host interactions for host health has been underlined by abundant experimental studies using gnotobiotic animal models. The morphology and functions of the immune system in germ-free animals differ from those in colonized animals. Organized immune structures, such as Peyer patches (PPs) and MLNs, are smaller in germ-free animals, contain lower numbers of B and T cells, and lack germinal centers. Furthermore, germ-free animals exhibit decreased