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Bridging immunity and lipid metabolism by gut microbiota

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Activity Objectives

1. To understand the relationship between the microbiota, the immune system, and environmental influences.
2. To identify proposed mechanisms by which metabolism affects the immune system.

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The human gut is a unique organ in which hundreds of different microbial species find their habitat and in which different host physiologic functions, such as digestion, nutrition, and immunity, coexist. Although all these players were studied separately for decades, recently, there has been an explosion of studies demonstrating the essential role for interactions between these components in gut function. Furthermore, new systems biology methods provide essential tools to study this complex system as a whole and to identify key elements that define the crosstalk between the gut microbiota, immunity, and metabolism. This review is devoted to several human diseases resulting from the disruption in this crosstalk, including immunodeficiency-associated and environmental enteropathies, celiac disease, inflammatory bowel disease, and obesity. We describe findings in experimental models of these diseases and in germ-free animals that help us understand the mechanisms and test new therapeutic strategies. We also discuss current challenges that the field is facing and propose that a new generation of antibiotics, prebiotics, and probiotics coupled with novel, systems biology–driven diagnostics will provide the basis for future personalized therapy. (J Allergy Clin Immunol 2013;132:253-62.)

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The human gut is a multifaceted organ. The most well-known functions of the gut are digestion, nutrient absorption, and secretion of hormones and enzymes that regulate food intake and metabolism throughout the body. These functions are largely mediated by intestinal epithelial cells, a single layer of epithelium that provides the barrier between the outside world and the body. The gut is also home to millions of resident microbes, which are termed the gut microbiota; as a whole, the microbiota genome has been estimated to contain 150-fold more genes than the host genome.[1] These microbiota contribute to nutrition and metabolism by processing and providing access to nutrients that would normally be inaccessible to the host. In addition to its role in metabolism, the gut is an important immune organ. The gut contains the largest lymphoid tissue mass in the body,[2] which might not be surprising considering the intestinal bacterial load. Thus in addition to contributing to host metabolism, the gut microbiota provides critical signals for the development of host immunity. Despite taking place in the same organ, historically, gut immune and metabolic functions were viewed and studied independently. More recently, however, systems approaches in research have uncovered intimate interactions between these 2 important functions, most of which involve a mediator: the gut microbiota. Disruptions of this intricate balance between host

Abbreviations used
CD: Crohn disease
CVID: Common variable immunodeficiency
IBD: Inflammatory bowel disease
SCFA: Short-chain fatty acid
TLR: Toll-like receptor

and commensal microbes have dramatic effects on human health and disease.

Germ-free animal models, which are completely devoid of microbiota, have been invaluable tools in understanding the contribution of the microbiota to host metabolic function. It has been demonstrated that the microbiota acts at many levels, from lipid processing and absorption to systemic lipid metabolism and storage.[3] Germ-free mice have increased fecal lipid and decreased serum lipid levels,[4] and formation and absorption of lipid droplets was reduced in the gut of germ-free zebrafish.[5] In addition to revealing these mechanisms of influence on local and systemic lipid metabolism, studies in germ-free mice have long demonstrated that the gut microbiota provides critical signals for the development of local and systemic immunity.[6-8] Germ-free mice have numerous immune defects, including low expression of antimicrobial peptides in the epithelium, reduced numbers and activation status of T lymphocytes, lower numbers of plasma cells, and impaired production of IgA. Importantly, in general, germ-free and antibiotic-treated mice have enhanced allergic reactions because they have increased numbers of eosinophils and basophils, increased local production of T_H2-associated cytokines, and increased IgE production.[9,10] In line with the hygiene hypothesis, early-life colonization was important to lessen the symptoms of allergic asthma and inflammatory bowel disease (IBD).[11]

In this review we will provide examples of clinical conditions involving alterations of both the metabolic and immune functions of the gut, examine animal models for studying these conditions, and discuss how these have helped reveal mechanisms for the interplay between the gut microbiota, immunity, and metabolism. We will also discuss current gaps in our understanding of the complex system that is the gut and how answering these questions will help to understand the pathogenesis and to guide the management of intestinal and systemic pathologies.

GUT MICROBIOTA CONTRIBUTES TO THE PATHOGENESIS OF ENTEROPATHY OF THE SMALL INTESTINE

Immunodeficiency-associated enteropathy

Since the first description in 1954, it has been recognized that human immunoglobulin deficiencies frequently present with disruptions in gastrointestinal function.[12] This suggests that there might be a connection between the 2 seemingly independent functions of immunity and absorption in the gut. Up to 50% of patients with common variable immunodeficiency (CVID), the most common symptomatic antibody immunodeficiency, present with gastrointestinal symptoms, including diarrhea, abdominal pain, lipid and sugar malabsorption, and steatorrhea (fatty stools), leading to decreased body mass index and low adiposity.[13-16] Similar symptoms are observed in many patients with secondary immunodeficiency caused by HIV/AIDS.[17,18] Histologic examination of the small intestine in both conditions shows intestinal villous atrophy, epithelial apoptosis, and inflammation.[13,19-23] In both cases of immunodeficiency, the enteropathy is often found in the absence of detectable pathogenic infections.[17,19] Interestingly, decreases in microbes that are beneficial to gut health,[24-26] including bifidobacteria and lactobacilli, are observed in patients with early-stage HIV, which might contribute to gut dysfunction.[27]

The differential response to therapies also provides evidence for the role of the gut microbiota in immunodeficiency-associated enteropathy. Although highly active antiretroviral therapy decreases the incidence of enteropathy, IgG antibody treatment for patients with CVID rarely ameliorates gut dysfunction, likely because IgA, but not IgG, antibodies are normally produced in response to the microbiota.[7,13]

The clinical symptoms of human immunodeficiencies suggest a connection between alterations in the immune system and changes in the metabolism and gut microbiota. Our group has recently described enteropathy in mice lacking B lymphocytes (BcKO mice),[28] demonstrating how in-depth analysis of a previously established model can reveal new information relevant for a human condition, which was missing an animal model. Indeed, we have found that BcKO mice have defects in fat absorption that are similar to those observed in patients with HIV and CVID, making them a useful model to study the mechanisms of immunodeficiency-associated gastrointestinal syndrome. The severity of this phenotype in mice is much milder than in human subjects, and no significant morphological alterations of the intestine are observed in BcKO mice. In the absence of apparent involvement of pathogens in mice (similar to the situation for CVID patients), the commensal microbiota is the most plausible trigger of immunity and IgA, which is produced by B cells and shown to be required for proper establishment of the gut microbiota.[29] Indeed, the investigation of both of these factors (microbiota by means of analysis of germ-free mice and IgA by means of analysis of IgA knockout mice) has confirmed that lack of IgA-mediated regulation of the microbiota is a mechanism behind fat malabsorption. Thus B-cell deficiency is a good example of complex interactions in which, affected by changes in adaptive immunity, the microbiota triggers innate immunity in the epithelium that downregulates fat transport, eventually leading to systemic changes, such as a decrease in overall fat amounts (Fig 1).

Examination of intestinal gene expression profiles revealed 2 clear effects: an increase in immune genes and a decrease in lipid metabolism and transport genes in the intestinal epithelium. Using promoter screening analysis, we revealed that genes from the decreased metabolic profile were enriched for GATA4, a key transcription factor for regulation of fat absorption in the small intestine.[30] However, it was unclear whether the metabolic impairment was related to immune activation and which cells were responsible for the latter. To address this question, we used a systems biology approach of gene network reconstruction and analysis. This analysis generated the model of gene regulation that was later supported by *in vitro* experimentation, suggesting that activation of immune (mostly interferon type I– and II–related) pathways in the epithelial cells leads to inhibition of metabolic gene expression (Fig 1). Interestingly, this interconnectedness of immunity and lipid metabolism has also been observed in macrophages in response to viral infection and IFN-γ, in which increased immune demand results in the downregulation of the sterol synthesis pathway.[31,32]

Furthermore, because of the high similarity in gene expression signatures in the intestine between B cell–deficient mice and