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ORIGINAL PAPERS

NATURAL MODULATION OF THE GUT MICROBIOTA IN PATIENTS WITH FOOD ALLERGIES

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Abstract. *In recent years, the intestinal microbiota has emerged as a significant contributor to the development of allergic diseases. Dysbiosis or microbial imbalance, can predispose individuals to allergies, while a balanced gut microbiome, fosters immune tolerance. The immune mechanisms involved in food allergies are complex and little is known about the possible role of the gut microbiota in the etiopathogenesis of food allergies. We hypothesized that the changes observed following diet therapy in food allergy would be associated with remission, rather than merely a response to diet that is independent of clinical outcome. Environmental factors such as urbanization, pollution, and dietary habits also significantly contribute to food allergies risk. It is not clear whether microbiota change in food allergies is an outcome of intestinal barrier defect or the cause of intestinal barrier dysfunction and inflammation. Manipulation of the gut microbiota as a method for modifying atopy, may be attempted in many ways including avoidance of certain foods, supplementation with probiotics and prebiotics, optimizing nutrient intake, minimizing stress, antimicrobial therapy, correction and prevention of low stomach acid, and fecal microbiota transplantation. The resident microbiota is important in maintaining structural and functional integrity of the gut and in immune system regulation. However, the precise mechanisms related to the effects of the microbiome on the pathogenesis of allergic diseases are unknown. Therapeutic diet ameliorates dysbiosis associated with food allergy and induces changes in the microbiome associated with remission. A better understanding of the disease mechanisms involved in allergic diseases is critical to develop prevention and treatment strategies. There was an increase of the intestinal permeability reported in patients with food allergies and a reduction of the gut microbiome diversity. Modifying gut microbiome during early years may be a preventive and therapeutic option in high-risk groups.*

Keywords: food allergies, host-microbiome interaction, immune regulation

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Adverse reactions to foods are extremely common, and generally they are attributed to allergy. The incidence of allergic disorders has been increasing over the past few decades, especially in industrialized countries. Allergies can affect people of any age. The pathogenesis of allergic diseases is complex and involves genetic, epigenetic, and environmental factors.

However, clinical manifestations of various degrees of severity related to ingestion of foods can arise as a result of a number of disorders, only some of which can be defined as allergic, implying an immune mechanism [1].

Food allergy is defined as “an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food” according to a 2010 Expert Panel Report supported by the National Institute of Allergy and Infectious Diseases. The prevalence of food allergies has increased worldwide in recent decades [2,3].

Food allergy is a clinical and public health problem that affects up to 10% of the world's children and 4% of adults, therefore the condition is highly prevalent with the gut microbiota having distinct roles. This review highlights recent progress in our understanding of the role of the gut microbiota in the development of food allergy [4,5].

Food allergies manifest in a variety of clinical conditions within the gastrointestinal tract, skin and lungs, with the most dramatic and sometimes fatal manifestation being anaphylactic shock.

In recent years, there has been increasing interest in how dysregulation of resident microbial communities (i.e. dysbiosis) may be associated with food allergy risk [6].

Food allergy is associated with alterations in the gut microbiota or dysbiosis early in life that may be predictive of disease persistence versus tolerance acquisition [7].

Gut dysbiosis likely precedes the development of food allergy, and the timing of such dysbiosis is critical. Gut microbiota may affect food allergy susceptibility by modulating type 2 immunity, influencing immune development and tolerance, regulating basophil populations, and promoting intestinal barrier function [8].

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Herein, we summarized the latest evidence on the gut microbiota profiles and functions associated with food allergy, oral tolerance mechanisms, and gut microbiota-targeted therapeutic strategies for food allergy.

Growing evidence has shown that a healthy gut microbiota contributes to protect against food allergy, whereas disruption of the gut homeostasis (dysbiosis) affects oral tolerance and confers susceptibility to food allergy [9,10].

The metabolites produced by the gut microbiota, such as short-chain fatty acids, tryptophan metabolites, and secondary bile acids, have favorable effects on food allergy [11-13]. In recent years, subsequent studies have shown that short-chain fatty acids exert multiple protective effects against food allergy.

The link between the microbiota and protection from food allergy is not well understood.

Recent research reveals that the increasing prevalence of food allergies is due in part to changes in the commensal microbiome [14].

Our understanding of food allergy has been advanced not only by studies of the microbiome, but also by findings from genome-wide association, transcriptome, epigenome, and metabolomic studies of food allergy.

By advancing research on the microbiome in food allergy, we can further our understanding of food allergy and derive new approaches for its prevention and therapy [15].

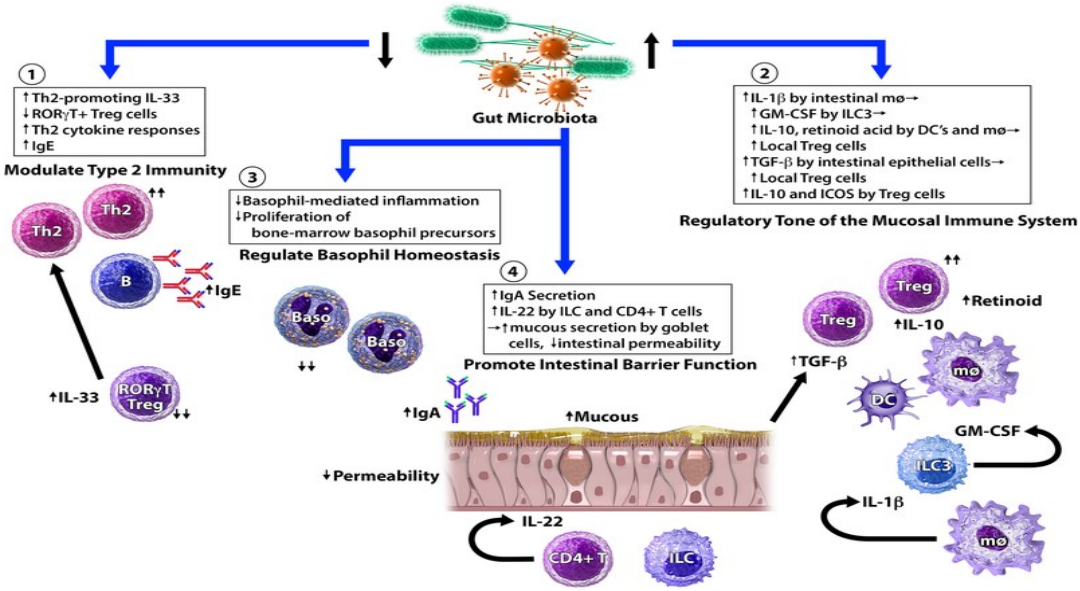

Figure 1. Mechanisms by which gut microbiota may affect food allergy susceptibility [8)

We have made significant progress in understanding the composition and function of the gut microbiota in food allergy, thanks to the advancements in genomic DNA sequencing technologies. The rise in the prevalence of food allergy over the past decades has focused attention of factors that may impact disease development, most notably the gut microbiota. By advancing research on the microbiome in food allergy, we can further our understanding of food allergy and derive new approaches for its prevention and therapy.

The cause of food allergy involves deviation from a default state of immune tolerance that is likely driven by antigen exposure, commensal microbiota, and their interactions [16].

The metabolites produced by the gut microbiota, such as short-chain fatty acids, tryptophan metabolites, and secondary bile acids, have favorable effects on food allergy. The primary byproducts of commensal bacteria's fermentation of complex and nondigestible carbohydrates, like dietary fibers, are short-chain fatty acids, which include acetate, propionate, and butyrate. Food allergy is caused by the loss of food-specific tolerance, a physiological immune reaction to ingested food antigens that have been modified by the gut microbiota [17].

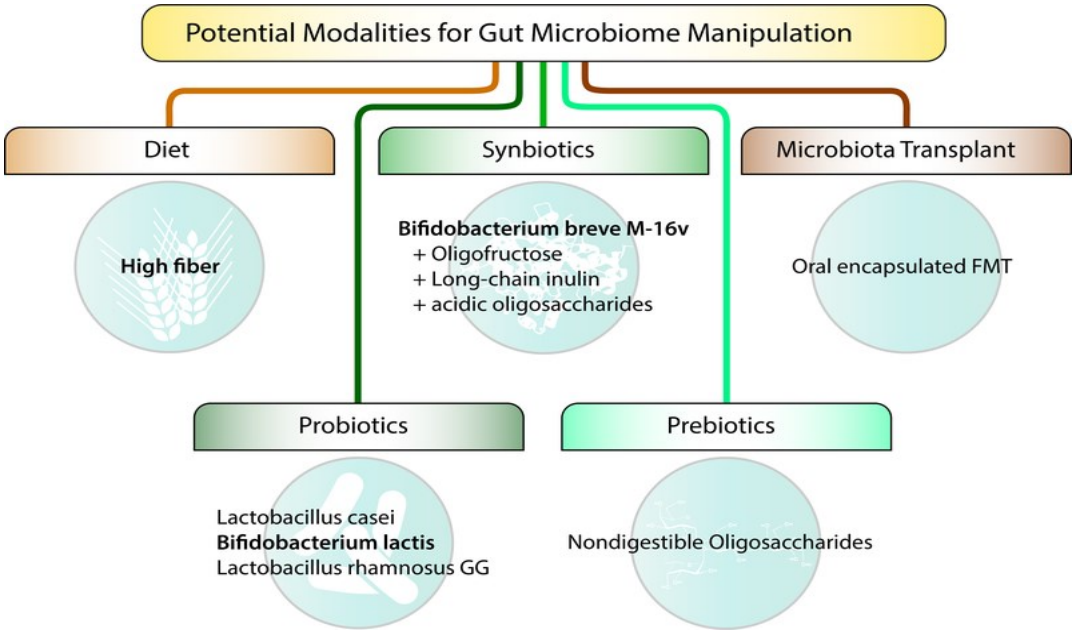

Figure 2. Potential modalities for gut microbiome manipulation [8)

Growing evidence supports a role for the gut microbiome in the pathogenesis and course of food allergy. Food allergies are divided into 2 main categories: IgE-mediated and non-IgE-mediated food allergies. IgE-mediated allergies are the best researched and documented. IgE-mediated and non-IgE-mediated food allergies represent a significant and growing challenge for the global healthcare system [18].

Recent research reveals that the increasing prevalence of food allergies is due in part to changes in the commensal microbiome. Th2/Th1 and Th17/Th1 ratio imbalances cause food allergy. Food allergy is modulated by intestinal microbiota. Food allergies reflect a hypersensitivity state induced by food allergens. However, causal relationships between intestinal microbiota and food allergy have indicated how food allergy are regulated by intestinal microbiota.

The stimulation of Treg cells is the main mechanism controlling immune tolerance to dietary antigens. Conversely, food allergy presents as a fast hypersensitivity in which IgE antibodies specific for food allergens attached to

basophils and mast cells cause the release of physiologically active mediators that cause allergy symptoms. The stimulation of allergen-specific T helper 2 (Th2) cells is the underlying immunological mechanism. The interplay between immune cells and the gut microbiota helps to maintain the balance between immune tolerance and food allergy. The role of the commensal microbiome in promoting tolerance and the connection between intestinal dysbiosis and food allergy are now being clarified. Research have demonstrated that the diversity, composition, particular species, and metabolites of the gut microbiota can significantly affect the maturation of immune responses to dietary antigens [19].

Dietary composition is also a key factor affecting intestinal microbiota. The gut microbiome likely plays a role in the pathogenesis and course of food allergy. Individuals with food allergy have different gut microbiomes compared to healthy controls [20,21].

Imbalances in the gut microbial ecosystem precede the development of food allergy, and the timing of such dysbiosis is a key factor [22,23].

Studies in humans have shown that compared with healthy controls, individuals have distinct gut microbiomes during the onset and progression of food allergy. Recent research reveals that the increasing prevalence of food allergies is due in part to changes in the commensal microbiome.

Mechanistic studies have established that the gut microbiota can affect the growth of immune tolerance to food antigens by modifying regulatory T cell differentiation, regulating basophil populations, and enhancing intestinal barrier function [24,25].

New therapeutic and preventive approaches to altering the gut microbiota using diet adjustments, probiotics, prebiotics, synbiotics, postbiotics, fecal microbiota transplantation [26-28,29].

Furthermore, we focused on the gut microbiota's potential role as a target for innovative strategies against food allergy. Ultimately, more studies are required to define the host-microbial relationship relevant to allergic disorders and amenable to new therapeutic interventions.

Conclusions

Gut dysbiosis likely precedes the development of food allergy, and the timing of such dysbiosis is critical. Gut microbiota associated with individual food allergies may be distinct. Our results demonstrated that the microbial composition was significantly different between food allergies patients and the healthy individual, which may be the reason leading to the various outcomes of probiotic treatment. This study suggests that disturbances in the gut microbiome composition and

metabolites and their crosstalk or interaction may participate in the pathogenesis of food allergies. By advancing research on the microbiome in food allergy, we can further our understanding of food allergy and derive new approaches for its prevention and therapy.

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