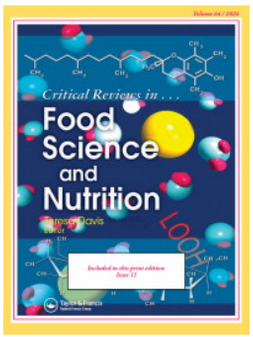

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REVIEW

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Gut microbiota: A target for prebiotics and probiotics in the intervention and therapy of food allergy

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ABSTRACT

Food allergy has become a major public health problem all over the world. Evidence showed that allergic reactions induced by food proteins often lead to disturbances in the gut microbiota (symbiotic bacteria). Gut microbiota plays an important role in maintaining the balance between intestinal immune tolerance and allergic reactions. Dietary intervention has gradually become an important method for the prevention and treatment of allergic diseases, and changing the composition of gut microbiota through oral intake of prebiotics and probiotics may serve as a new effective adjuvant treatment measure for allergic diseases. In this paper, the main mechanism of food allergy based on intestinal immunity was described firstly. Then, the clinical and experimental evidence showed that different prebiotics and probiotics affect food allergy by changing the structure and composition of gut microbiota was summarized. Moreover, the molecular mechanism in which the gut microbiota and their metabolites may directly or indirectly regulate the immune system or intestinal epithelial barrier function to affect food immune tolerance of host were also reviewed to help in the development of food allergy prevention and treatment strategies based on prebiotics and probiotics.

KEYWORDS

Food allergy; gut microbiota; prebiotics; probiotics; bacteria-gut axis

Introduction

Food allergy has become a major public health problem, which seriously threatens the health of people and hinders the global economic and social development. Approximately 8% of children and 5% of adults are allergic to one or more kinds of food reactions from milk, eggs, sesame, wheat, peanuts, nuts, fish, and shellfish, and most food allergies are type I hypersensitivity reactions caused by allergens, which are mainly mediated by IgE (Barni et al. 2020; Verhoeckx et al. 2015). One of its main characteristics is the imbalance of T-helper cell type 1/T-helper cell type 2 (Th1/Th2), which is expressed as a tendency of the immune response toward the Th2 type (Hong et al. 2020; Jiang et al. 2019; Wang et al. 2021). Once the allergenic food is ingested by susceptible people, allergic reaction occurs within few minutes (Davis et al. 2019; Ekezie, Cheng, and Sun 2018). This condition is accompanied by different allergic symptoms, such as itching, vomiting, diarrhea, urticaria and dyspnea, and is even life-threatening.

Recently, the development of gene sequencing and muti-omics technologies has provided a new method to further study the human symbiotic microbiota, especially in the aspect of alleviating food allergies through the regulation of gut microbiota. The composition of gut microbiota (symbiotic bacteria) may affect the balance between intestinal immune tolerance and allergic reactions (Arrieta et al. 2014, 2015). The risk of allergic diseases increases when the reduction of microbial exposure is reduced in the early life (Arpaia et al. 2013; Marrs et al. 2021; Tordesillas, Berin, and Sampson 2017). Both clinical studies and experimental animal models have suggested that food allergies are intervened by regulating the gut microbiota. Moreover, food allergies are related to the structure of gut microbiota as well as the intestinal metabolites. The metabolic spectrum of mice significantly changes before and after peanut allergy intervention (Chalcraft et al. 2014). In addition to the changes in biomarkers including histamine and leukotriene C4, the metabolites such as phosphatidylcholine and lysophosphatidylcholine also changed substantially. Furthermore, among the metabolites of many gut microbiotas, short-chain fatty acids (SCFAs) are one of the most important markers (Tan et al. 2016). Studies have shown that SCFAs regulated food allergy by activating pathways through G protein-coupled receptors, inhibiting histone deacetylase activity and enhancing the protective effect of the intestinal epithelial barrier (Mckenzie et al. 2017).

Probiotics are important for intestinal microbiome. Oral probiotics can alter the gut microbiota by adhering to the mucosa and by colonizing the colon, which provides the most direct way to improve gut microbiota (Ruiz-Moyano et al. 2019). Gut microbiota can also be improved using

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prebiotics, which are not digested or absorbed by the host gastrointestinal tract, but it selectively promotes the colonization (Leblanc et al. 2017). In addition, the metabolites produced by gut microbiota through prebiotics enhances human health and the prevention of various diseases (Khangwal and Shukla 2019; Mohanty et al. 2018; Xie et al. 2019). Prebiotics and probiotics regulate the balance of gut microbiota and have the advantage of high safety, the use of microorganisms (prebiotics, probiotics and synbiotics) for the prevention and treatment of food allergy has become a hot research topic and favored by the patients suffering from food allergy.

Mechanisms of food allergy and oral tolerance based on intestinal immunity

Mechanisms of food allergy

Food allergy refers to the intestinal hypersensitivity to common foods, which is caused by the failure of body to establish or destroy the constructed oral tolerance (Figure 1). After food allergens enter orally the gastrointestinal tract, antigen-presenting cells such as dendritic cells (DCs) capture the antigen and present it to Th0 cells in the lymph nodes. Activated Th0 cells differentiate into Th2 cells in the presence of IL-4, and a series of cytokines such as IL-4, IL-5 and IL-13 secreted by Th2 cells stimulate B cells to differentiate into plasma cells, produce specific antibody IgE, and induce humoral immune response (Tordesillas, Berin, and Sampson 2017). In addition, Th2 cells promote the secretion of IL-4 by mast cells and basophils to activate B cells. Moreover, IL-4 and IL-5 promote the activation and proliferation of eosinophils and mast cells, as well as the mucus secretion of goblet cells. The antigen-specific IgE secreted by B cells binds to the high-affinity FcεRI receptor expressed on the surfaces of mast cells and basophils, placing the body in a sensitized state. When the body is exposed to allergens again, the antigen immediately binds to the specific IgE on the surface of sensitized mast cells or basophils, induce mast cells to degranulate, and release bioactive substances such

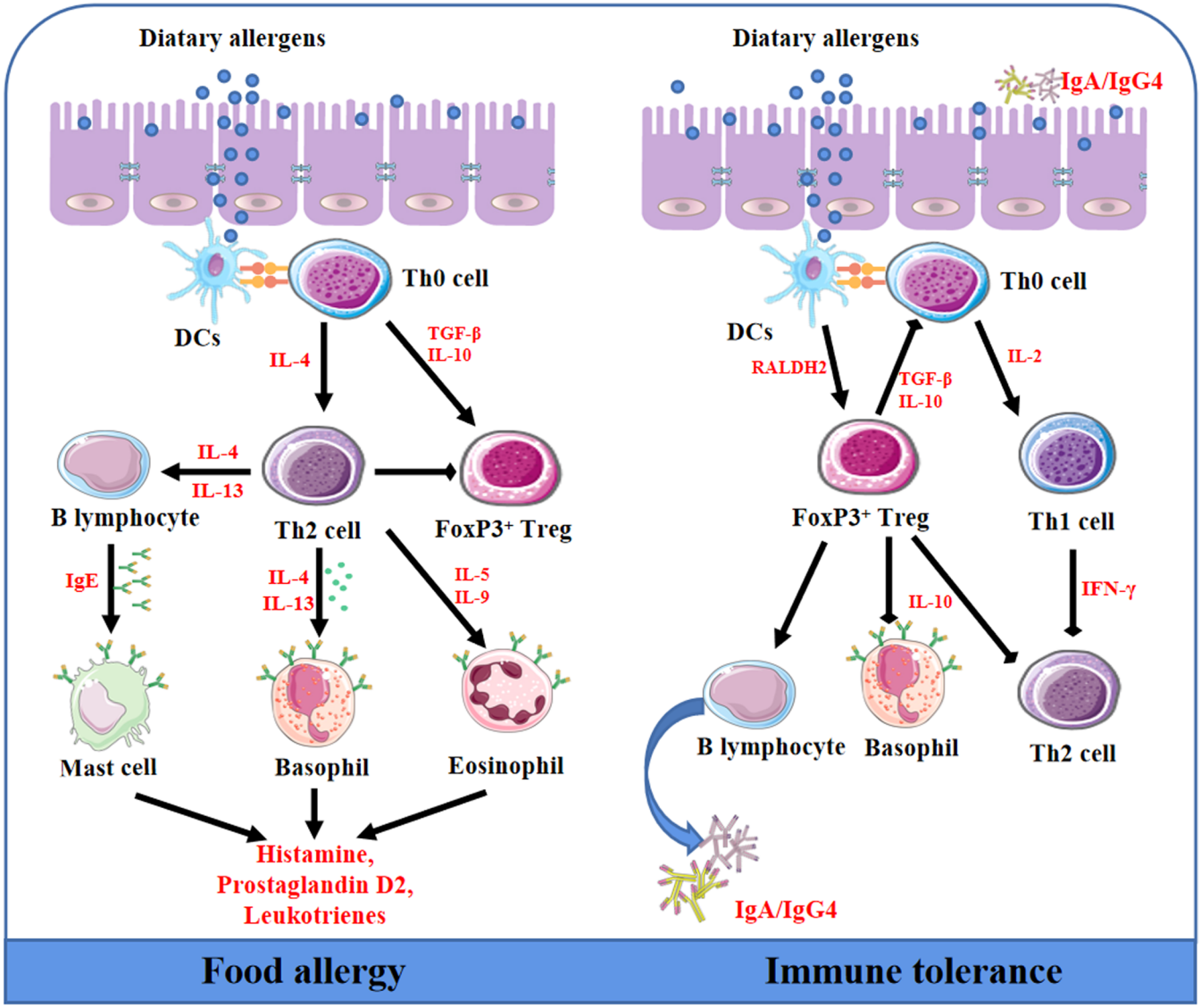

Figure 1. Mechanisms of IgE-mediated food allergy based on intestinal immunity. Th1, T-helper-1; Th2, T-helper-2; DC, dendritic cell; IL, interleukin; Ig, immunoglobulin; IFN-γ, interferon gamma; TGF-β, transforming growth factor-beta; ⟶ indicates promotion; ⟙ indicates inhibition.

as histamine, prostaglandin D2 (PGD2) and leukotrienes (LT), which further cause local or systemic allergic reactions.

However, recent studies have found that bone marrow cells in peanut-allergic individuals such as monocytes and neutrophils are also involved in the early stages of food allergy (Alcántara-Hernández and Idoyaga 2021). After a brief exposure to peanut allergens, the monocytes, DCs, and neutrophils were activated in the peripheral blood of peanut allergic patients in addition to basophils (Tordesillas, Berin, and Sampson 2017). Similarly, Toll-like receptor (TLR) 4 and monocytes were activated in peripheral blood monocytes of egg allergic patients (Kosoy et al. 2016). Many researchers have found the different phenomena in animal models sensitized by different allergen. So far, no comprehensive and definitive conclusion has been made on the mechanism of food allergy, and further studies are still needed.

Oral tolerance

Oral tolerance is a state of specific immune unresponsiveness of the body to food established by the gut-associated lymphatic system. DCs are one of the most studied cells in food allergy, and they are extremely important in the process of establishing oral tolerance. $CD103^+$ DCs migrate to secondary lymphoid tissues after antigen recognition. Transcriptional growth factors and retinoic acid (RA) expressed in the draining lymph nodes induce the differentiation of initial T cells into FoxP3-expressing regulatory T cells (Tregs) to promote mucosal tolerance and suppress allergic responses (Ma et al. 2019; Mazzini et al. 2014; Scott, Aumeunier, and Mowat 2011). Retinoic acid (RA) secreted by $CD103^+$ DCs induces the Treg expression of integrin α4β7, thus promoting the produce of $Foxp3^+$ Treg and suppressing immune response (Bakdash et al. 2015). Mouse models have demonstrated that the RA-induced expression of integrin α4β7 on the surface of T cells is closely associated with T cell-mediated oral tolerance (Cassani et al. 2011). $CD103^+$ DCs may also induce differentiation of $CD4^+$ T cells into type I Tregs, and Tr1 cells do not express Foxp3 and can secret IL-10. Therefore, $CD103^+$ DCs are considered to be a major subpopulation of DCs related to mucosal tolerance (Pabst and Mowat 2012). It has been shown that $CCR9^+$ DCs in lymphoid tissues can induce the production of Treg, thereby suppressing the development of antigen-specific immune responses (Hadeiba et al. 2008).

Treg cells are also important immune cells that regulate the immune response of the body, and they play an important role in avoiding the damage caused by excessive immune response to the body (Johnson, Jing, and Orentas 2007). It has been shown that healthy people are more tolerant to allergens than allergic patients, mainly because of the presence of more Treg cells in healthy people (Palomares et al. 2017, 2010). Tregs usually express CD4, CD25 and the transcription factor Foxp3, and secrete cytokines such as IL-10 and TGF-β to inhibit the proliferation and activation of Th0 cells, and Treg also has inhibitory effects on Th1, Th2, Th17 and basophils (Fontenot, Gavin, and Rudensky 2003; Tan et al. 2016). Furthermore, $Foxp3^+$ Treg promotes B cells to produce IgA/IgG4, thus affecting the binding of IgE to allergens (Uchida and Okazaki, 2017). IgA/IgG4 is transported to the intestinal cavity to maintain immune tolerance (Iweala and Burks, 2016). Human clinical studies have shown that Tregs from patients with some degree of immune tolerance after oral immunotherapy exhibit the hypomethylation of the Foxp3 locus, indicating that the transcript levels of Foxp3 is increased, supporting that Treg is associated with oral tolerance (Iweala and Burks, 2016). However, the molecular mechanisms of oral tolerance in normal individuals are not well studied, and related research will also be one of the focuses in food allergy.

Gut microbiota and food allergy

Intestinal micro-ecosystem is composed of gut microbiota and its living environment, and gut microbiota is the core component. At present, nine phyla have been detected in the intestine, including *Firmicutes, Bacteroidetes, Proteobacteria, Actinobacteria, Verrucomicrobia, Fusobacteria, Cyanobacteria, Spirochaeates* and *VadinBE97*. Among these phyla, *Firmicutes* and *Bacteroidetes* are the predominant microflora, accounting for 90% of the gut microbiota (van den Elsen et al. 2017). Intestinal microbiota in healthy individuals is beneficial to host health and is closely associated with pathogen suppression, nutrient absorption, host metabolism, and the immune system modulation. Furthermore, the gut microbiota has co-evolved with humans, and multiple interactions between the host and microbiome are necessary to maintain the health of the human body.

Diet on gut microbiota

The composition of gut microbiota is affected by various factors in the living environment with the growth of human age, showing a dynamic change (Brown et al. 2012; Roduit et al. 2014). To some extent, dietary intake is a key determinant for the diversity and functionality of intestinal symbiotic bacteria. Dietary patterns (Western diet, Eastern diet and Mediterranean diet) have different effects on intestinal microbial composition (Laudisi, Stolfi, and Monteleone 2019; Sakkas et al. 2020). In comparison with Western diets patterns with high sugar, fat and protein, Eastern and Mediterranean diets are vegetarian and rich in dietary fiber, plant polysaccharide and polyphenols (Moszak, Szulińska, and Bogdański 2020). Diets rich in polyphenols and dietary fiber can promote the reproduction of beneficial intestinal bacteria, such as *Lactobacillus* and *Bifidobacterium*, and inhibit the growth of *Bacteroides* and *Clostridium histolyticum* (Sun et al. 2018). Based on the study of the relationship between changes in dietary composition and gut microbiota, the gut microbiota of mice changed reproducibly and reversibly after the consumption of a high-fat and high-sugar diet, and the results of animal experiments were also verified in the later clinical experiments (Carmody et al. 2015). Recent studies agreed that vegetarian diet enhances the composition of gut microbiota. Moreover, the short-term consumption of a diet composed entirely of animal or plant products

Table 1. Clinical study on composition and diversity of intestinal microbiota in IgE-mediated food allergy.

Types of food allergy	Sample number	Influence on gut microbiota	References
Cow's milk	n = 226	*Clostridia*, *Firmicutes* ↓, *Bacteroidetes*, *Enterobacter* ↑	(Bunyavanich et al. 2016)
	n = 39	*Bacteroides*, *Alistipes* ↑, *Streptococcaceae*, *Enterobacteriaceae* ↓	(Berni Canani et al. 2018)
	n = 60	*Bifidobacteriaceae*, *Ruminococcaceae* ↓, *Lactobacillaceae* ↑	(Dong et al. 2018)
	n = 17	*Coriobacteriaceae* ↓	(Díaz et al. 2018)
Egg	n = 141	*Ruminococcu*, *Lactococcu*, *Leuconostoc* ↑	(Fazlollahi et al. 2018)
Cow's milk, egg, wheat, soy, walnut, peanut	n = 216	*Citrobacter*, *Oscillospira* ↓, *Lactococcus*, *Dorea* ↓	(Savage JH, 2018)
Peanut	n = 1879	*Clostridiales* ↓, *Bacteroidales* ↑	(Huang et al. 2016)
Milk, egg, peanut, soy, wheat, walnut	n = 225	*Bifidobacterium*, *Clostridium* and *Haemophilus* ↓	(Savage et al. 2018)
Peanut	N = 1422	*Bacteroidetes* ↓ *Enterobacteriaceae/Bacteroidetes* ↑	(Tun et al. 2021)
Egg white, cow's milk, wheat, peanut, soybean	n = 23	*Firmicutes*, *Proteobacteria*, *Firmicutes*↑, *Bacteroidetes* ↓	(Chen et al. 2016)
Milk, peanut, treenut, egg, sesame	n = 309	*Bacteroidetes*, *Proteobacteria* ↓, *Firmicutes*, *Actinobacteria* ↑	(Goldberg et al. 2019)
Egg, wheat, soybean, cow's milk, peanut, shrimp, crab	n = 8	*Akkermansia*↓, *Veillonella* ↑	(Inoue et al. 2017)
Tree nuts, fish, milk, egg, soy	n = 68	*Oscillibacter valericigenes*, *Lachnoclostridium bolteae* and *Faecalibacterium* sp ↑	(Kourosh et al. 2018)
Cow's milk, egg, wheat, nut, peanuts, fish, shrimp, soybean	n = 34	*Bacteroidetes*, *Proteobacteria* and *Actinobacteria* ↓ *Firmicutes* ↑	(Ling et al. 2014)

↑ indicates increase or high levels; ↓indicates decrease or low levels.

changed the structure of the volunteer microbial community and overcame the influence of the differences in microbial gene expression among individuals (David et al. 2014). Studies on the intestinal microbial composition of healthy adults with vegetarian diet proved that the *Bacteroidetes* at the phylum level was increased and the abundance of *Prevotella* was higher at the genus level (Losno et al. 2021). Therefore, dietary intervention is important to improve the structure of gut microbiota in the later life of host. It is also a problem that cannot be ignored by immunization clinical researchers.

Intestinal microbial disorders and food allergy

The initial explanations for the relationship between gut microbiota and allergic diseases were the "hygiene hypothesis" and the "intestinal flora hypothesis." The classical hypothesis is that in highly industrialized places, both the living environment and lifestyle are relatively clean, which greatly avoids the exposure to microorganisms. Meanwhile, the heavy use of antibiotics and vaccination causes Th1 dysfunction in the body and weakens the immune function of the body. Consequently, the immune system develops a tendency to allergic response, and the body is in an allergic state, thus increasing the incidence of allergic diseases. Therefore, the composition of gut microbiota plays an important role in the development of immunity, and it is a key factor in regulating food allergy (Prince et al. 2015).

Data from allergic population studies showed that gut microbiota between food allergic patients and healthy donors are different (Table 1). IgE-mediated food allergy has specific microbial community characteristics. Goldberg et al. demonstrated that the abundance of *Bacteroidetes* and *Proteobacteria* decreased, while the abundance of *Firmicutes* and *Actinobacteria* increased in the human intestines of milk, peanuts, eggs, nuts and sesame allergy (Goldberg et al. 2019). Infants and children with food allergies have a different gut microbiological composition. A birth cohort study in infants with a family history of allergies showed an increase in *Streptococcus* and a decrease in *Bifidobacterium* in the gut microbiota at 1 week and 1 month (Goldberg et al. 2019). Throughout infancy, the continuous low abundance of *Bacteroidetes* and high ratio of *Enterobacteriaceae*/*Bacteroidetes* increased the risk of food allergen sensitization, thus increasing the risk of peanuts allergy, which proved the evidence that food allergy is caused by the changes in intestinal microbial composition (Tun et al. 2021). Further studies found that the children with food allergy enriched specific microorganisms in *Clostridia* class and *Firmicutes phylum* (*Oscillobacter valericigenes*, *Lachnoclostridium bolteae*, *Faecalibacterium* sp.) (Kourosh et al. 2018). Meanwhile, *Ruminococcus*, *Lactococcus* and *Leuconostoc* were enriched in the intestinal tract of children with egg allergy (Fazlollahi et al. 2018). By contrast, adults with allergies have low gut microbiota diversity, high abundance of *Bacteroidales*, and low abundance of *Clostridiale* (Huang et al. 2016).

In comparison with IgE-mediated food allergy, limited reports have focused on the composition and diversity of intestinal microorganisms in non-IgE mediated food allergy. Wang et al. observed that microbial imbalance related to non-IgE mediated milk protein allergy had a destructive effect on intestinal immune tolerance and homeostasis (Wang et al. 2021). A study showed that gut microbiota may also play a role in non-IgE-mediated food allergy (Mennini et al. 2020). Berni et al. showed that the imbalance of gut microbiota in children with non-IgE mediated milk allergy was caused by the enrichment of *Bacteroides* and *Listeria* (Berni Canani et al. 2018). However, the imbalance of gut microbiota in non-IgE- and IgE-mediated milk allergic children had the same characteristics, such as an increase in *Bacteroides*. Therefore, the regulation of intestinal flora balance should be the main strategy of dietary intervention for food allergy in clinical studies.

Human cohort studies on food allergy belong to qualitative observations. The relationship between gut microbial composition and the development of food allergy can be explored by studying the mechanism of food allergy based on many mouse model. Germ-free (GF) mice, a classical animal model, has become the first choice for the study of gut microbiota, and the related technologies have become quite sophisticated (Smith, Mccoy, and Macpherson 2007). In comparison with normal mice, GF mice showed stronger sensitivity, higher levels of mast cell protease-1 and beta-lactoglobulin (BLG)-specific immunoglobulin G1 (Rodriguez et al. 2011). Similarly, the lack of gut microbiota significantly enhanced the BLG-specific immune response in BALB/c mice (Hazebrouck et al. 2009). A fecal microbiota transplantation (FMT) mouse model showed that the allergic symptoms of GF mice induced by β-lactoglobulin was improved after the GF mice received FMT from healthy subjects, which may be attributed to the presence of cystic anaerobes in the intestine (Feehley et al. 2019). Further, the feces from healthy children were transplanted into GF mice, the mice were able to tolerate the attack of allergens, and the healthy gut microbiota of children were successfully colonized in GF mice. By contrast, the intestinal microorganisms from children with food allergies were transplanted into sterile animals, resulting in more serious allergic reactions when this xenotransplantation mouse was challenged with allergens (Di Costanzo, De Paulis, and Biasucci 2021).

Prebiotics

Prebiotics were first proposed by G. R. Gibsion in 1995 (Gibson and Roberfroid 1995). In 2016, the concept of prebiotics was redefined as "healthy substrate for the selective utilization by host microorganisms" in the International Association for Prebiotics and Probiotics Sciences (Gibson et al. 2017). Prebiotics are not digested or absorbed in the stomach, but they promote the proliferation of probiotics in the intestine. The metabolites produced by intestinal probiotics such as acetic acid and lactic acid interact with host cells and immune system to regulate the health of the host. Currently, prebiotics mainly includes functional oligosaccharides, such as fructooligosaccharides (FOS), xylooligosaccharides (XOS), galactooligosaccharides (GOS), isomaltooligosaccharides (IMO), soybean oligosaccharides (SBOSs), polysaccharides (e.g., Spirulina and Spirulina), protein hydrolysates, polyols, and some natural plants, such as vegetables, Chinese herbal medicine, and wild plants (Chang et al. 2018; Krumbeck et al. 2018; Li et al. 2015; Singh et al. 2017).

Probiotics

The Food and Agriculture Organization of the United Nations and the World Health Organization (FAO/WHO) define probiotics as "living microorganisms that bring health benefits to the host when administered at sufficient doses" (Hill et al. 2014). Probiotics colonize the body, change the composition of the host's gut microbiota, regulate the immune function by affecting the balance of the intestinal microecology, inhibit the reproduction of pathogenic bacteria, promote the absorption of nutrients, and maintain intestinal health (Kim et al. 2019). Currently, the most researched probiotics mainly include *Lactobacillus* and *Bifidobacterium*.

Regulation of gut microbiota by prebiotics and probiotics

Human gut is a highly active metabolic organ composed of living microorganisms, and it provides metabolic, immune, and protective functions for the body through the interaction between the microbiota and the host. Ingestion of prebiotics or probiotics may have a positive impact on the composition and metabolism of human gut microbiota in the small intestine and colon (Mujagic et al. 2017; Yan et al. 2013).

Prebiotics regulate the gut microbiota

Prebiotics can promote the growth and reproduction of intestinal beneficial bacteria in vivo, form the competitive advantage of microecology, optimize the balance of intestinal microecology, and improve immunity, which further maintain the health of the body (Quigley 2019). Prebiotics promote the proliferation of intestinal beneficial bacteria (e.g., *Bifidobacterium* and *Lactobacillus*), while the metabolism of SCFAs and antibacterial substances produced by beneficial bacteria can directly inhibit the growth and reproduction of exogenous pathogenic bacteria and intestinal spoilage bacteria (e.g., *Bacteroides*, *Clostridium* and *Escherichia coli*), and maintain the health of the organism (Peredo-Lovillo, Romero-Luna, and Jimenez-Fernandez 2020; Serrano-Villar et al. 2017). The intake of prebiotics such as GOS, resistant starch, low FOS, and inulin can significantly increase the number of Bifidobacterium in infants and adults (Finegold et al. 2014). Based on the study of the dose-dependent effect of low-galactose on gut microbiota in healthy adults, the minimum daily dose of 5 g GOS significantly changed the gut microbiota of healthy adults, mainly increasing the number of *Bifidobacterium* (Sierra et al. 2015). Similarly, SBOSs reduced the abundance of *Enterococcus* and increased the abundance of *Bifidobacillus* and *Lactobacillus* in a cyclophosphamide immunosuppressive mouse model (Ma et al. 2020).

Probiotics regulate the gut microbiota

As a kind of live microorganism beneficial to the host, probiotics is crucial for the establishment of a healthy gut microecosystem. Probiotics have a healthy effect on the human body by changing the composition of the gut microbiota, and it may also provide a new method in the treatment of intestinal diseases such as diarrhea, constipation, and gastrointestinal infections (Lee et al. 2019; Mai et al. 2021; Wang et al. 2020; Wen et al. 2020; West et al. 2020).

Table 2. Prebiotics and probiotics regulate the gut microbiota composition.

Prebiotics/Probiotics	Experimental subjects	Influence on gut microbiota	References
Prebiotics			
XOS	Healthy adult subjects (n = 32)	*Bifidobacterium* ↑	(Finegold et al. 2014)
Inulin	Healthy adult volunteers(n = 12)	*Bifidobacteriumadolescent* ↑	(Ramirez-Farias et al. 2008)
GOS	Healthy term infants (n = 365)	*Bifidobacterium* ↑	(Sierra et al. 2015)
	Prefrail elderly (n = 20) and healthy adults (n = 24)	*Bifidobacteria* ↑, *microbial diversit* ↓	(Wilms et al. 2021)
XOS	Rats fed a high-fat diet	*Firmicutes* and *Bacteroidetes* ↑	(Fei et al. 2019)
	Eighty pigs	*Proteobacteria*, *Citrobacter* ↓, *Firmicutes*, *Lactobacillus* ↑	(Pan et al. 2019)
SBOSs	Cyclophosphamide immunosuppressive mice.	*Bifidobacillus* and *Lactobacillus*↑, Enterococcus ↓	(Ma et al. 2020)
Probiotics			
Lactobacillus rhamnosus GG	Healthy infants (n = 20) and cows milk allergy infants (n = 19)	*Blautia*, *Roseburia*, *Coprococcus* and *Oscillospira* ↑	(Berni Canani et al. 2016)
LGG-TMC0356-fermented milk	Subjects were collected before and after treatment with probiotics (n = 14) and without probiotics (n = 11)	*Bacteroidetes/Firmicutes* ratio ↓	(Harata et al. 2017)
Bifidobacterium bifidum TMC3115	cow's milk protein allergy (n = 256)	*Lactobacillus*, *Alistipes* and *Barnesiella* ↑	(Wei, Liu, and Wang 2020)
Lactobacillus acidophilus	β-lactoglobulin induced allergic mice model	*Lachnospiraceae*, *Ruminococcaceae* and *Bacteroidales* ↑	(Ni et al. 2020)
Lactobacillus rhamnosus, *L. salivarius* LA307, *Bifidobacterium longum* subsp	β-lactoglobulin induced mice model	*Prevotella* ↑, *Marvinbryantia* ↓	(Esber et al. 2020)

↑ indicates increase or high levels; ↓indicates decrease or low levels.

Animal experiments and clinical studies have confirmed that the intake of exogenous probiotic fermented milk and preparations renovate the intestinal microecological balance and enhance the immuno-modulatory function of the intestine (Kawashima et al. 2011; Villena et al. 2011). In a randomized double-blind control trial, after six-month intervention on cow's milk protein allergy with *Bifidobacterium bifidum* TMC3115, the gut microbiota testing revealed that *Bifidobacterium*, *Lactobacillus*, *Turicibacter*, *Sutterella*, and *Parabacteroides* were the most predominant phylum (Wei, Liu, and Wang 2020). Moreover, in the mice model sensitized by β-lactoglobulin, the oral administration of *Lactobacillus acidophilus* KLDS 1.0738 improved the richness and diversity of fecal microbiota, which was characterized by fewer *Proteobacteria phylum* and *Helicobacteraceae* family, and higher *Firmicutes phylum* and *Lachnospiraceae* family (Ni et al. 2020). Further studies confirmed that oral litchi juice fermented by *Lactobacillus casei* affected the gut microbiota of mice induced by cyclophosphamide, as evidenced by the remarkable increase in the relative abundance of *Firmicutes phylum*, as well as the genera of *Faecalibaculum*, *Lactobacillus*, and *Akkermansia* (Wen et al. 2020).

Table 2 summarizes the data that intake of some prebiotics and probiotics may have a positive impact on the composition and metabolic function of gut microbiota in the small intestine and colon. However, prebiotics and probiotics regulate gut microbiota in different ways. Probiotics, as an oral supplement, should contain sufficient numbers of live microorganisms to alter the host flora and have potential health benefits. Prebiotics, a food for intestinal beneficial bacteria, can improve the survival rate of probiotics in the intestine. Therefore, synbiotics, a combination of prebiotics and probiotics, play a synergistic role in regulating the gut microbiota to jointly play a beneficial role in the health of the host. At present, synbiotics has been widely used in obesity, human ulcerative colitis, irritable bowel syndrome and other diseases (Astó et al. 2019; Nazila Kassaian et al., 2020; Sergeev et al. 2020). Notably, synbiotics also prevent and treat food allergies. It was reported that the fermented milk supplemented with probiotics and prebiotics effectively altered the gut microbiota and immunity of host animals (Wang et al. 2020). Another study showed that isomalto-oligosaccharides cooperated with *Lactobacillus* transferred the balance of Th1/Th2 to Th1, which was beneficial to enhancing the defensive ability of the host immune system (Mizubuchi et al. 2005). Similarly, the post-sensitization administration of non-digestible oligosaccharides (scFOS and lcFOS) and *Bifidobacterium breve* M-16V reduced allergic symptoms in mice (van Esch et al. 2016). Although the combination of prebiotics and probiotics can achieve a synergistic effect, the intrinsic mechanism of regulation of intestinal flora structure after the synergistic effect of both is still unclear, thus requiring further research.

Prebiotics and probiotics regulate food allergy through the bacteria-gut axis

Prebiotics regulate food allergy

Prebiotics is a new substance that can alleviate intestinal immune diseases and play acrucial role in the prevention of allergic diseases (Table 3). FOS, as the most widely studied prebiotics, is used for the intervention and treatment of food allergies. Results showed that the diet supplemented with FOS reduced acute allergic symptoms and mast cell degranulation upon challenge and prevented the challenge-induced increase in whey-specific IgE as observed in sensitized mice (Vonk et al. 2017). Moreover, the number of mast and $CCR4^+$ cells was reduced, and the formation rate of duodenal edema was significantly inhibited in

Table 3. Immunomodulatory effect of prebiotics on food allergy.

Prebiotics	Experiment model	Main results	References
FOS	Cow' s milk induced mouse model	Allergic symptoms and mast cell ↓, sIgE level ↑	(Vonk et al. 2017)
	OVA induced mouse model	IFN-γ$^+$IL-4$^+$ CD4$^+$ T cells and CD45RBhighCD69$^+$CD4$^+$ T cells ↑, IFN-γ ↑	(Tsuda et al. 2017)
	OVA induced mouse model	Mast cells and the edema rate ↓	(Fujitani et al. 2007)
Raffinose and stachyose	OVA induced mouse model	IgE, IgG1, mMCP-1, IL-4 ↓ and Tregs ↑	(Yamashita et al. 2021)
Isomaltodextrin	OVA induced mouse model	Specific IgE, IgG ↓, IL-12, Tregs ↑	(Mine et al. 2019)
Guar gum and cellulose	Peanut induced mouse model	*Bacteroïdes*, *Lactobacillus* and *Bifidobacterium* ↑; *Firmicutes* ↓ and SCFAs ↑	(Tan et al. 2016)
HMOs	β-lactoglobulin induced mouse model	IgE ↓, IL-10, TGF-β, and IFN-γ ↑, *Lactobacillus* ↑, *Lactococcus* and *Alistipes* ↓	(Liu et al. 2020)

↑ indicates increase or high levels; ↓ indicates decrease or low levels.

OVA-induced allergic mice fed with FOS (Fujitani et al. 2007). Similarly, the dietary intake of FOS during the development of food allergy attenuated the induction of intestinal Th2 cytokine responses by regulating early activation of naive CD4(+) T cells (Tsuda et al. 2017).

In human cohort study, randomized trials and observational studies followed up for at least 4 weeks showed that dietary intake of prebiotics (FOS, GOS) reduced the risk of food allergy (Cuello-Garcia et al. 2017). In a multicenter, randomized, double-blind and placebo-controlled trial among 365 healthy full-term infants, the feeding of infant formula containing GOS produced a significant prebiotic effect, including changes in fecal composition and microbiota, as well as changes in fecal consistency and the frequency of defecation. Moreover, during the scGOS/lcFOS intervention period, infants had significantly lower incidence of allergic manifestations (Arslanoglu et al. 2008). Thus, prebiotics perform their physiological functions mainly through their interaction with beneficial gut microbiota, suggesting that the combined use of prebiotics and probiotics may play a synergistic role in regulating food allergy.

Probiotics regulate food allergy

Probiotics are a group of active microorganisms that are beneficial to the host, and they can colonize the human intestinal tract and reproductive systems to produce the effect of health to improve microecological balance of the host and exert beneficial effects. Probiotics have been reported to promote antigen degradation or structural modification in the intestine, regulate the secretion of pro-inflammatory factors and promote normalization of abnormal microflora in the intestine. Therefore, many researchers have considered whether probiotics can be used to regulate intestinal flora for the prevention and treatment of food allergies (Tang and Lu, 2019).

Many clinical experiments proved that different probiotics have different protective effects against allergies caused by different foods (Table 4). *Lactobacillus rhamnosus* GG (LGG) is the most widely used probiotics in allergy clinical trials. Berni et al. showed that the addition of LGG to the diet of milk-allergic infants reduced the incidence of allergic symptoms and accelerated the acquisition immune of tolerance in infants, indicating that LGG has a therapeutic effect on allergy (Berni Canani et al. 2017; Berni Canani et al. 2012). Another study by Berni et al. showed that *Blautia*, *Roseburia* and *Coprococcus* were significantly enriched following treatment with LGG, but only one genus, *Oscillospira*, had a significant difference between the infants who became tolerant and those infants who remained allergic. These data showed that LGG promoted the tolerance in infants with CMA to a certain extent by affecting the bacterial community structure at the strain level in the infants' intestines (Berni Canani et al. 2016). In a multicenter, randomized, double blind, placebo controlled study, Cukrowska et al. (Cukrowska et al. 2021) found that the mixture of probiotic strains (*Lactobacillus rhamnosus* ŁOCK 0900, *Lactobacillus rhamnosus* ŁOCK 0908 and *Lactobacillus casei* ŁOCK 0918) improved the score of atopic dermatitis in children with cow's milk protein allergy. This finding indicates that mixed strains can also improve allergy symptoms.

Yang et al. screened three strains of *Lactobacillus*, namely, *Lactobacillus acidophilus*, *Lactobacillus plantarum* subsp. *Plantarum*, and *Lactobacillus delbrueckii* subsp. *bulgaricus* by co-culturing *Lactobacillus* with mouse splenocytes in vitro, which have the potential intervention ability against soybean allergy (Yang et al. 2021). Animal models also provide strong evidence that probiotics regulate food allergies. In an OVA-induced mouse allergic model, the intervention of *Lactobacillus pentosus* S-PT84 significantly alleviated the clinical allergenic symptoms and reduced the levels of histamine and mMCP in serum (Majumder et al. 2020). Moreover, *Lactobacillus plantarum* suppressed OVA-induced allergy by inhibiting the production of IL-4, IL-5 and IL-13 cytokines and the activation of mast cells (Huang, Lin, and Jan 2017). Meanwhile, both *Lactiplantibacillus plantarum* and *Lactobacillus rhamnosus* suppressed the expression of specific antibodies and cytokines in OVA-induced BALB/c mice (Mizuno, Ohto, and Kuwahara 2021; Shin and Kim 2019). In addition, in a β-lactoglobulin-induced allergic mouse model, the oral administration of *Lactobacillus delbrueckii subsp. bulgaricus* CRL 656 remarkably reduced the secretion of IL-4 and increased the secretion of IL-10, IL-17A, and IL-6 (Pescuma et al. 2019). Therefore, probiotics can achieve a therapeutic

Table 4. Immunomodulatory effect of probiotics on food allergy.

Probiotics	Experiment subject/mouse model	Main results	References
L. rhamnosus GG	Infants with milk allergy (n = 220)	Obtained greater tolerance at ages 12, 24, and 36 months after received the formula plus probiotic combination	(Berni Canani et al. 2017)
L. rhamnosus GG	Infants with cow's milk allergy (n = 39)	Enriched the *Blautia* and *Roseburia* in tolerant infants; Promoted the production of higher fecal butyrate levels	(Berni Canani et al. 2016)
L. rhamnosus GG	Children (1-10 years) with peanut allergy (n = 62)	achieved desensitization about 89.7% of subjects who received the combination treatment	(Tang et al. 2015)
L. rhamnosus GG	Children with milk protein allergy (n = 55)	Increased rates of milk allergy resolution after 6 and 12 months	(Berni Canani et al. 2012)
L. rhamnosus GG	Children with cow's milk protein allergy (n = 100)	improved the symptoms of bloody stool, diarrhea, restiveness and abdominal distension	(Basturk et al. 2020)
Bifidobacterium infantis CGMCC313-2	OVA induced allergic asthma and β-lactoglobulin induced mice models	Inhibited the secretion of IgE IL-4 and IL-13	(Liu et al. 2017)
Clostridium butyricum CGMCC0313-1	β-lactoglobulin induced mice model	Improved intestinal allergy symptoms, increased SIgA, $CD4^+CD25^+Foxp3^+$ cells, Th1/Th2 and Th17/Treg cells balance	(Zhang et al. 2017)
Bulgaricus CRL656	BLG induced mice mouse	Increased IL-10, INF-γ, IL-6, and IL-17A, decreased IL-4	(Pescuma et al. 2019)
Lactococcus lactis	Ara h 2 protein induced mice model	Increased SIgA, Th1 cytokines and Treg level	(Ren et al. 2014)
Lactiplantibacillus plantarum 22 A-3	OVA induced mice model	Decreased total IgE and OVA-specific IgE	(Mizuno, Ohto, and Kuwahara 2021)
Lactobacillus pentosus S-PT84	Egg induced mice model	Reduced the total IgE, IgG, histamine, mMCP levels, IL-4 and IL-17, increased the population of $CD25^+Foxp3^+$cells	(Majumder et al. 2020)
Lactobacillus murinus AB326349	OVA induced mice model	Promoted immune balance shifted from Th2 to Th1, reducing mast cell activation and serum IgE production in mice, as well as allergic diarrhea	(Huang et al. 2016)
Lactobacillus plantarum	OVA induced mice model	Inhibited IL-4, IL-5, IL-13 and IL-17A production, and reduced Th2-related genes expression in the small intestine and Th2 response	(Huang, Lin, and Jan 2017)
Lactobacillus rhamnosus	OVM induced mice mouse	Decreased the IgA, IgG1 and IgG2a	(Shin and Kim 2019)

effect on allergies at the immune level. Overall, probiotics regulate food allergy symptoms mainly by regulating the cellular homeostasis (including Th1/Th2, Th17/Treg) and immunoglobulin production (including IgE, IgG1, IgG2a, and IgA) in allergic mice, in terms of antibody and cytokine secretion, and cell differentiation, but the exact relationship between the regulation of food allergy by probiotics and the structural changes of the gut microbiota is still inconclusive, thus requiring further investigation.

Furthermore, many reports have focused on the use of a combination of *lactobacillus* strains to intervene allergic reactions. In OVA-induced allergic mice the mixture of probiotics (*Lactobacillus Gallis* LK001, *Lactobacillus salivarius* LK002, *Lactobacillus Johnson* LK003, *Lactobacillus paracasei* LK004, *Lactobacillus royei* LK005, and *Bifidobacterium* animal LK011) alleviated the allergic symptoms by inducing the activation of mucosal $CD103^+$ DCs, thus promoting the differentiation of Tregs and regulating the composition of gut microbiota (Ma et al. 2019). Another study showed that in OVA-stimulated and challenged mice, the oral administration of the mixture of *Lactococcus lactis* KF140, *Pediococcus pentosaceus* KF159, *Lactobacillus pentosaceus* KF340, *Lactobacillus paracasei* 698 and *Bacillus amyloliquefaciens* 26 N significantly inhibited the allergic reaction, decreased the rectal temperature, reduced the level of IgE and the secretion of Th2 cytokines (IL-4, IL-5 and IL-13) and Th17 cytokines (IL-17), and induced the proliferation of $CD4^+Foxp3^+$ Tregs (Shin et al. 2018). Therefore, probiotics can effectively alleviate food allergic reactions by regulating the composition of the intestinal flora. However, probiotic intervention in food allergy is strain-specific, and not all strains have anti-allergic effects.

Microbiome-gut-immune axis regulate food allergy

The intestine is not only an important place for digestion, absorption and nutrient exchange but also the largest immune organ of the human body. The intestinal tract contains a large number of symbiotic microorganisms, which maintain a relatively stable microecological balance in the host through symbiosis or antagonism. Diet structure and composition directly affect intestinal structure and function, as well as the composition of the gut microbiota and the diversity of its metabolites. The intestinal mucosa plays an essential role in immune function through contact with antigenic substances in foods. Many studies have confirmed the mechanism of dietary intervention (prebiotics and probiotics) based on microbiome-gut-immune axis in regulating food allergy (Figure 2).

Gut microbiota regulates mucosal immunity

Commensal bacteria that colonize the mammalian gut affect Th2-mediated inflammatory responses and allergic diseases. The dysbiosis of intestinal microecology leads to the enhancement of retinoic acid (RA) signal in mucosal dendritic cells ($CD103^+$) and induces food allergy (Wu et al. 2022). After dendritic cells were activated by antigen, they promoted the expression of retinal dehydrogenase 2 (RALDH2), and produced conduction signals, such as RA, induced the differentiation of Th0 cells into Th1 cells or $Foxp3^+$ Treg (Caminero et al. 2019). Intake of probiotics can change the balance of intestinal micro-ecology and thus regulate food allergies. Oral administration of Lactobacillus has been reported to activate mucosal $CD103^+$ DCs, thereby promoting the differentiation of regulatory Tregs, and increasing the proportion of the *Deferribacteres* and

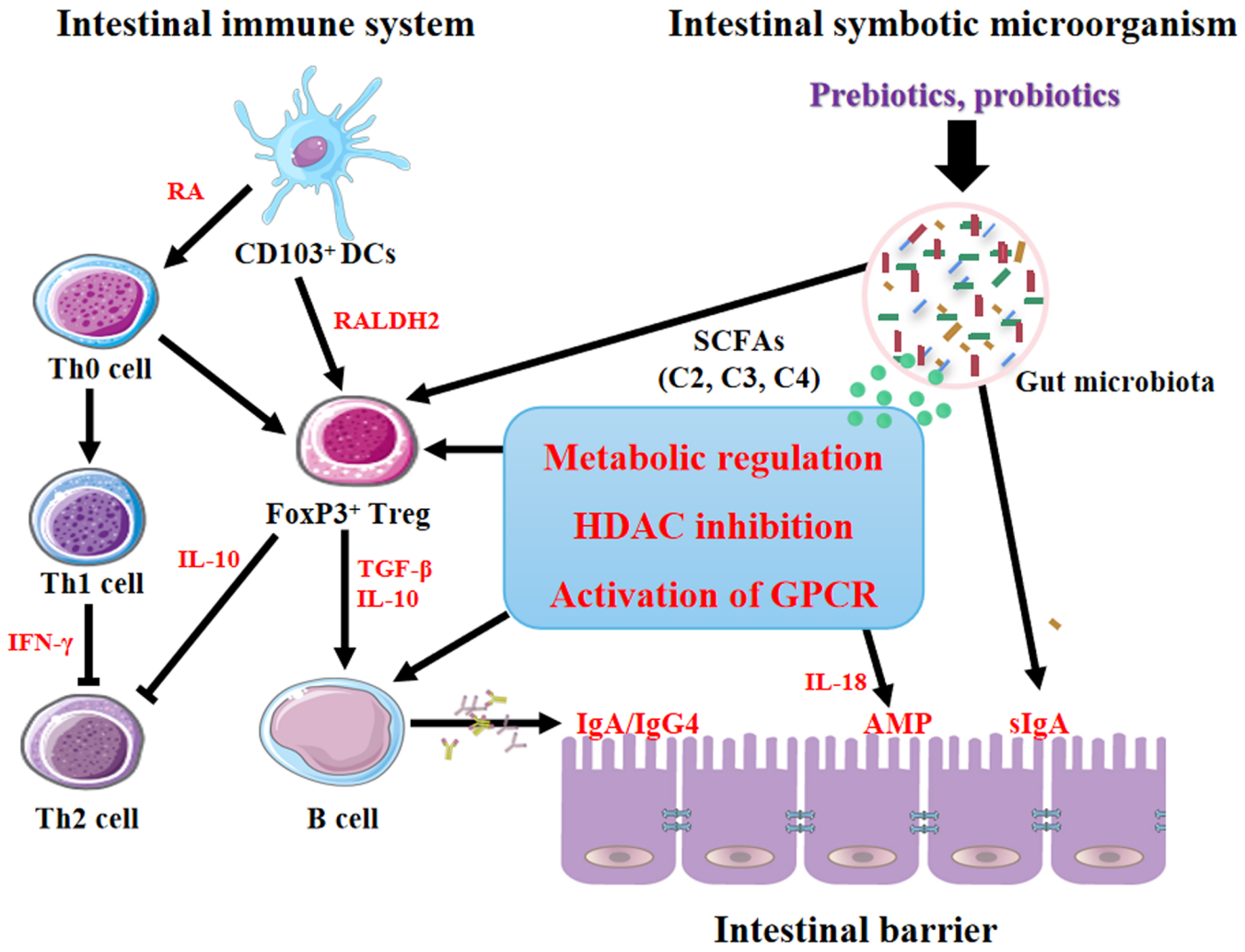

Figure 2. Mechanism of dietary intervention on food allergy by regulating intestinal microecological balance. Th1, T-helper-1; Th2, T-helper-2; DC, dendritic cell; IL, interleukin; Ig, immunoglobulin; GPRs, G protein coupled receptors; HDAC, histone deacetylase; IFN-γ, interferon gamma; TGF-β, transforming growth factor-beta; ⟶ indicates promotion; ⊣ indicates inhibition.

Verrucomicrobia phyla, as well as the *Mucispirillum* and *Clostridium* XlVa genera (Ma et al. 2019). In another study, *Lactobacillus* induced T helper (Th) 1 or Treg differentiation to inhibit Th2-biased response for regulating Th1/Th2 immune balance (Yang et al. 2021). Furthermore, in the study of intestinal mucosal immune homeostasis, IL-10 and TGF-β secreted by Foxp3⁺ Treg can also inhibit the differentiation of Th2 cells, maintain the balance of intestinal mucosal immune system, and stimulate the B cells to secrete more IgA and IgG4 into the intestinal cavity to maintain immune tolerance (Slack, Balmer, and Macpherson 2014). In addition, sIgA regulates the composition of the intestinal microbiota and participates in maintaining a balanced relationship between the gut microbiota and the immune system of host (Li, Jin, and Chen 2020; Vernocchi, Del Chierico, and Putignani 2020). Some researchers have found that some specific probiotics have the effect of regulating intestinal flora structure and intestinal mucosal immunity, but the question of whether the probiotic effect of these probiotics is transient or has a sustained effect remains unknown.

Intestinal microbes strengthen the intestinal epithelial barrier via IL-22

IL-22 can be produced only by blood cells, but its receptors are produced by intestinal epithelial cells in mucosa, playing an important role in the communication between immune cells and intestinal epithelial cells (Sabat, Ouyang, and Wolk 2014). Gut microbiota interacts with immune cells (DCs, macrophages, and innate lymphocytes) to promote the production of IL-22 and strengthen the barrier function of intestinal epithelial cell (Iweala and Burks 2016). As described in 7.3.1, CD103⁺ DCs play a crucial role in the generation and maintenance of oral tolerance. However, CD103⁺ DCs can receive microbial signals such as flagellin to produce IL-23, thereby inducing other cells to produce IL-22 and affecting epithelial cell function (Feehley and Nagler, 2014). Among the different types of innate lymphocytes, ILC2 can produce Th2-type cytokines to exacerbate food allergy, while RORγt⁺ ILC3 can produce IL-22 to reinforce intestinal epithelial cell function and promote the secretion of antimicrobial peptides (such as REG3β and mucus).

Gut microbiota metabolites regulate food allergies

The gut microbiota and its metabolites are closely related, and their interaction plays an important role in the immune system. The dietary metabolites of food in the intestine can transmit signals to the body that modulate the body's immune response (Francavilla et al. 2012). Dietary prebiotics and other nutrients were digested and degraded by beneficial intestinal bacteria to produce small molecules, such as short-chain fatty acids (SCFAs), which participated in various metabolic pathways of the body. SCFAs are a source of energy for colonic cells. It entered the cells as histone deacetylase inhibitor via monocarboxylate transport proteins and transmitted signals via G protein-coupled receptors (Feehley and Nagler 2014). The binding of SCFAs to GPRs acts on intestinal epithelial cells to activate inflammatory vesicles to mature IL-18 and promote the secretion of antimicrobial peptides (AMP), which can strengthen intestinal integrity and repairing epithelial cell damage. SCFAs can stimulate the DCs directly to promote the differentiation of initial T cells into $Foxp3^+$ Treg, and also acts directly on $Foxp3^+$ Treg to promote their self-proliferation (Chinthrajah et al. 2016). In the allergic model of mice induced by peanut extract, Tan et al. showed that the serum total IgE level was decreased in allergic mice after the oral administration of SCFAs, while more severe allergic reactions were observed in SFCA receptor knockout mice (Tan et al. 2016). Moreover, microbiota metabolite SCFA acetate promoted intestinal IgA response, which was mediated by metabolite-sensing GPR43 (Wu et al. 2017). In addition, butyrate upregulated the expression of genes related to histone acetylation modification, promoted the production of Tregs, and maintained the immune homeostasis of the body (Hao et al. 2021).

In summary, the composition of the gut microbiota and metabolites can be altered by dietary prebiotics or probiotics, while gut microbiota and metabolites interact with the mucosal immune system. Thus, dietary intervention can affect the development of immune tolerance and food allergy through the microbiota-gut-immune axis.

Conclusions and prospect

Prebiotics and probiotics can improve the microecological balance of the host, alter the composition of the gut microbes, and regulate the host's immune response. Many studies agreed that intestinal microorganisms play an important role in the pathogenesis of food allergy. Especially in early life, the structure and composition of intestinal commensal bacteria have an important effect on the metabolism of the host, the maturation of immune system and the development of oral tolerance. Animal models and clinical trials have demonstrated the direct and indirect effects of prebiotics and probiotics on gut microbiota, immune system and epithelial barrier. Changes in the composition of the gut microbiota can affect the composition of its metabolites, such as SCFAs, secondary bile acids, amino acid derivatives, and other small-molecule metabolites, which also directly or indirectly affect the regulatory function of the immune system. Therefore, the dietary intake of prebiotics and probiotics can alleviate the symptoms of food allergy and enhance the tolerance of the body to allergic foods by restoring gut microbiota and mucosal immune balance. It is the most common food allergy intervention method, which is suitable for allergic patients of any age group. It aims to reconstruct the gut microbiota for allergic disorders and restoring a healthy micro-ecosystem.

However, the effect of probiotics has obvious strain specificity and dose dependence, and different strains require different doses to play a role, and even the same strain may require different doses for different diseases, which needs further experimental and clinical evaluation. Considering that prebiotics provide substrates for the growth of probiotics, probiotics are in a favorable position in the competition with intestinal symbiotic bacteria, and the effect of prebiotics is strengthened. Therefore, the synergistic effect of single strain or mixed probiotics and prebiotics will become a very promising measure for the prevention and treatment of allergic diseases in the future.

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