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Review Article

Gut Microbiota Promotes Immune Tolerance by Regulating RORγt$^+$ Treg Cells in Food Allergy

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Food allergy is a significant public health problem troubling people, and the incidence has been on the rise in the past decade. Emerging evidence suggests an influence of the gut microbiota in susceptibility to food allergies. Epidemiological studies have shown an association between altered exposure to the microbiome and the risk of food allergies. Intervention of the gut microbiota in germ-free mice or supplementation of probiotics can regulate the proliferation of regulatory T (Treg) cells in mice and inhibit food allergy by promoting the expression of receptor-associated orphan γt$^+$ (RORγt$^+$) regulatory T (Treg) cells and inhibiting the proliferation of T helper 2 (Th2) and Th17 cells. This paper reviews the current research progress on how the gut microbiota enhances immune tolerance to prevent food allergy through RORγt$^+$ Treg, hoping to provide some new ideas and effective targets for the prophylaxis of food allergy.

1. Introduction

Common allergic disorders include food allergy (FA), asthma, allergic rhinitis, atopic dermatitis, Henoch-Schönlein purpura, urticaria, eczema, and drug allergy [1]. After asthma and allergic rhinitis, food allergy has become a new public health issue [2, 3]. In recent years, many epidemiological reports on FA have painted a grim picture [4]. A great deal of data show that the prevalence of FAs is increasing [5]. Many studies report that FAs are becoming more common, increasingly children and adults are being diagnosed with FAs, and it takes longer than previously thought for people to build immune tolerance to no longer be allergic to food [4] and hospitalizations for FAs are increasing [5]. In addition, FAs were once thought to be more common in developed countries, but they may now be more prevalent in developing countries, which is thought to be because of genetic factors [6].

The mucosal surface is often invaded by a variety of microorganisms, so it has a strong intestinal mucosal immune system and various immune cells with potent activity [7]. There are many different populations of lymphocytes in the mucosal lamina propria, such as IgA-secreting plasma cells, γδ T cells, dendritic cells (DC), and innate lymphocytes (ILC). They play an important role in resistance to pathogen infection and maintenance of mucosal barrier function. Among them, regulatory T (Treg) cells play a central part in maintaining immune tolerance and homeostasis in the whole body, especially intestines [8]. Treg cells expressing receptor-associated orphan γt$^+$ (RORγt) are a specialized subset of CD4$^+$Foxp3$^+$ cells in the gut. Studies have shown that the expression of RORγt in Tregs is beneficial to improve its inhibitory ability during intestinal specific immune response, making Foxp3$^+$RORγt$^+$ T cells become an important effector Treg subset in the intestinal system [9, 10]. Lochner et al. [11] found that 20–30% of Foxp3$^+$ T cells express RORγt in the gut lamina propria (LP), and such a high proportion depends on the complex gut microbiota.

In recent years, people have become increasingly interested in studying the function of the gut microbiota and its role in intestinal mucosal immunity [12]. In the situation of urbanization and industrialization, the increasing incidence of allergic diseases worldwide has led to research into the influence of corresponding environmental and dietary

factors that may be associated with the development of allergies [10]. Epidemiologic studies demonstrate that changes in the commensal microbiota act an important role in FA susceptibility. Human cohort studies suggested that individuals with FAs had a different gut microbiome compared to healthy control subjects, and dysbiosis preceded the development of FAs [13]. This article mainly reviews the potential part of the gut microbiota in the evolution of FA and discusses how the gut microbiota affects the immune tolerance through the regulation of RORγt$^+$ Treg cells.

2. Gut Microbiota and Food Allergies

FA is one of the most common allergic diseases characterized by adverse immune reactions and hypersensitivity to food proteins [14, 15]. In recent years, the prevalence of FA has risen worldwide. It has been confirmed that the imbalance of the gut microbiome during infancy is one of the most important factors causing FA [16–18]. Gut microbiota may play a significant role in the pathogenesis of FA [18].

2.1. Characteristics of Gut Microbiota in People with Food Allergies. FA is closely related to gut microbiota-related diseases, and changes in the number and types of symbiotic microbiota may lead to various diseases in and outside the gastrointestinal tract. The gut microbiota directly participates in the development of innate and acquired mucosal immune responses. The four major phyla in the human gut microbiome are *Firmicutes*, *Bacteroidetes*, *Proteobacteria,* and *Actinobacteria* [19]. *Bacteroidetes* and *Firmicutes* account for more than 90% of the total colonic bacteria, and *Actinomycetes* and *Proteobacteria* are usually less abundant (<1–5%) [20, 21]. Compared with healthy individuals, allergic populations have reduced gut microbiota diversity [17, 22], exhibiting relatively higher abundances of *Firmicutes*, *Proteobacteria*, and *Actinobacteria* at the phylum level [23]. At the genus level, the proportion of *Clostridium* belonging to *Firmicutes* is more abundant, while the proportion of *Bacteroides* belonging to *Bacteroidetes* is relatively low in people with food allergies [22, 23]. In addition, *Enterococcus*, *Escherichia coli*, *Shigella*, *Staphylococcus*, *Faecalibacterium*, *Anaerobic bacteria*, and *Prevotella* were more frequently detected in people with food allergies than in healthy people [22, 23]. Table 1 shows the specific changes in intestinal microbiota between food allergic and normal subjects shown in these studies.

2.2. Association between Gut Dysbiosis and Allergy Risk. The pathways of gut microbiota affecting food allergy sensitivity may include regulating type 2 immunity, affecting immune system maturation and immune tolerance, modulating basophil populations, and promoting intestinal barrier function [21, 28]. The dynamics between immune tolerance and allergic responses may be mediated by interactions between the symbiotic microbiota and the innate and acquired mucosal immune systems [29]. Treg responses and mucosal IgA induced by symbiotic bacteria are essential for maintaining host microbial homeostasis and preventing intestinal mucosal inflammation [30]. First, the gut microbiome promotes IgA secretion, which helps reduce the absorption of allergens. Second, microbial colonization of *Clostridia* (mainly clusters XIVa and IV) induced the production of IL-22 by innate lymphocytes and CD4$^+$ T cells. The cytokine IL-22 protects the intestinal epithelial barrier by promoting goblet cell mucus secretion and reduces intestinal permeability to food allergens [31]. In addition, RORγt$^+$ Tregs express high levels of interferon regulatory factor 4 (IRF4), conferring Tregs the ability to inhibit T helper cell 2 (Th2) receptors [32]. Studies have highlighted that infants with a significant imbalance of microbiota among their gut (known as "dysbiosis") may be at increased risk of allergic diseases [33]. Many studies using animal models have described mechanisms by which specific bacterial taxa within the gut microbiota may promote oral tolerance [34–36]. The dysbiosis of gut microbiota, including *Clostridium* and *Bacteroides* [30], impedes the differentiation of naïve T cells into RORγt$^+$ iTreg cells. iTreg cells with a Th2-cell-like phenotype expanded, characterized by increased GATA3 expression and IL-4 secretion [37]. These pathogenic Treg cells are unable to inhibit mast cell activation or Th2 cell expansion, resulting in a dysregulated FA response, accompanied by dietary allergen-specific IgE responses, and impaired barrier integrity [38] (Figure 1). These findings suggested that the balance of gut microbiota could maintain immune tolerance and prevent allergic inflammation. In turn, the imbalance of gut microbiota may increase the risk of food allergy [39–41].

3. Immune Tolerance Mediated by RORγt$^+$ Treg

3.1. Differentiation and Function of Treg Cells. Tregs are considered important regulators of a broad range of immune responses, including allergic diseases, inflammation, autoimmunity, and responses to microorganisms and tumors. As such, they command the activity of most cell types of the innate and acquired immune system [42]. Foxp3$^+$ Treg cells consist of two distinct developmental subpopulations: thymus-derived Treg cells (tTreg) and peripheral derived Treg cells (pTreg), which derive from naive T cells generated in the thymus and develop into Foxp3 expressing cells [43, 44].

The differentiation program of thymus-derived regulatory T (tTreg) cells is initiated by T cell receptor (TCR) signaling caused by thymic presentation of autoantigens, allowing the transcription factor REL to enter the nucleus. REL binds to the conserved noncoding sequence 3 (CNS3) and Foxp3 promoter with several other transcription factors to induce Foxp3 gene expression [45, 46]. The tTreg cells move to the gut and experience further functional ripening and respond to environmental incentives. pTreg cells differentiate from naive CD4$^+$T cells and occur in the gut in a stepwise manner similar to tTreg cells. The differentiation of pTregs is mediated by microbial antigen-induced TCR signaling as well as transforming growth factor-β (TGFβ) and retinoic acid-mediated signaling. These signals promote the binding of REL to CNS3 and the binding of SMAD3 and the retinoic acid receptor (RAR)-retinoic acid X receptor (RXR) to CNS1 of Foxp3 [7, 47].

Table 1: Comparison of changes in intestinal microbiota between food allergic and normal subjects.

Source organism	Features of gut microbial community		Reference
	Decrease	Increase	
Human	*Bacteroidetes* (P), *Bacteroides* (G), *Parabacteroides* (G), *Prevotella* (G), *Alistipes* (G), *Streptococcus* (G), *Veillonella* (G), *Bacteroides* (S), *Prevotella* (S), and *Veillonella* (S)	*Firmicutes* (P), *Actinobacteria* (P), *Proteobacteria* (P), *Sphingomonas* (G), *Sutterella* (G), *Bifidobacterium* (G), *Collinsella* (G), *Clostridium sensu stricto* (G), *Clostridium IV* (G), *Enterococcus* (G), *Lactobacillus* (G), *Roseburia* (G), *Faecalibacterium* (G), *Ruminococcus* (G), *Subdoligranulum* (G), *Akkermansia* (G), and *Subdoligranulum* (S)	[19]
Human	*Bacteroidetes* (P)	*Firmicutes* (P)	[22]
Human	*Bacteroidetes* (P), *Proteobacteria* (P), *Actinobacteria* (P), *Verrucomicrobia* (P), *Bacteroides* (G), *Streptococcus* (G), *Veillonella* (G), *Klebsiella* (G), *Blautia* (G), *Clostridium XI* (G), *Lachnospiracea incertae sedis* (G), and *Megasphaera* (G)	*Firmicutes* (P), *Fusobacteria* (P), *Enterococcus* (G), *Escherichia/Shigella* (G), *Lactobacillus* (G), *Staphylococcus* (G), *Faecalibacterium* (G), *Clostridium XIVa* (G), *Anaerostipes* (G), *Prevotella* (G), *Clostridium XVIII* (G), and *Flavonifractor* (G)	[18]
Human	*Leuconostoc* (G)	*Firmicutes* (P), *Verrucomicrobia* (P), *Ruminococcus* (G), *Lactococcus* (G), and *Leuconostoc* (G)	[24]
Human	*Bifidobacterial* (G) and *Enterobacteria* (G)	*Lactobacilli* (G)	[13]
Human	*Leuconostoc* (G), *Weissella* (G), and *Veillonella* (G)	*Clostridium* (G)	[25]
Mouse	*Firmicutes* (F), *Erysipelotrichi* (C), *Erysipelotrichales* (O), and *Erysipelotrichaceae* (F)	*Proteobacteria* (P), *Gammaproteobacteria* (C), *Enterobacteriales* (O), and *Enterobacteriaceae* (F)	[26]
Mouse	*Verrucomicrobia* (P) and *Proteobacteria* (P)	*Bacteroidetes* (P) and *Patescibacteria* (P)	[27]

The increased/decreased microbiota in food allergic group when compared with normal group.

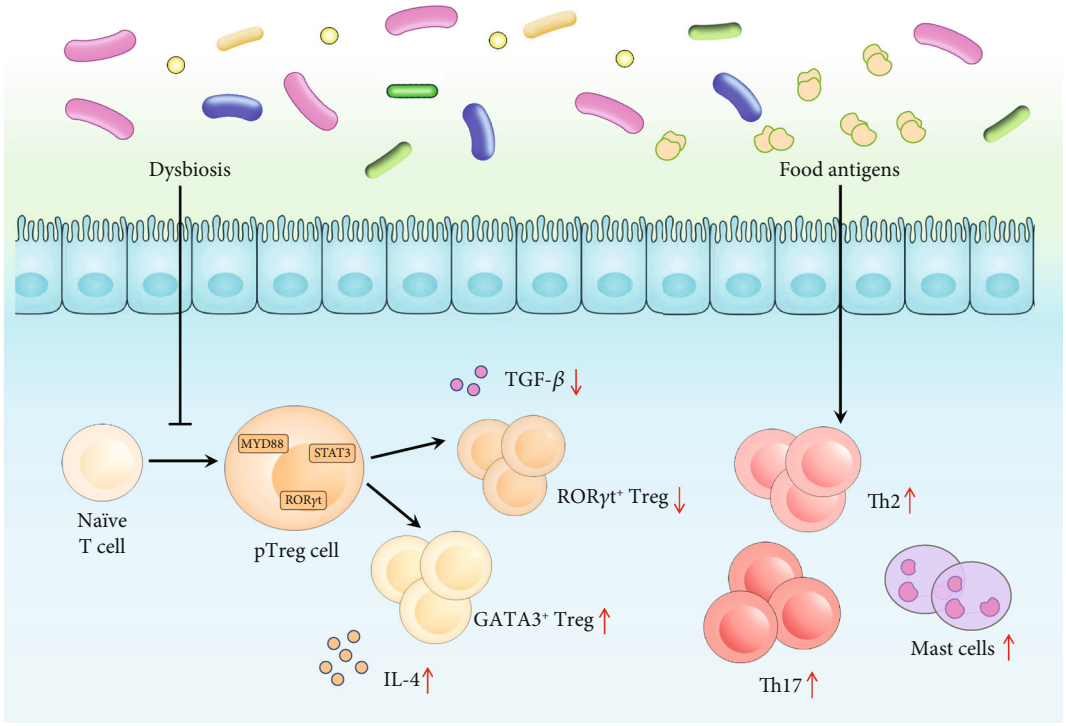

Figure 1: Overview of RORγt+ Treg cells in food allergies.

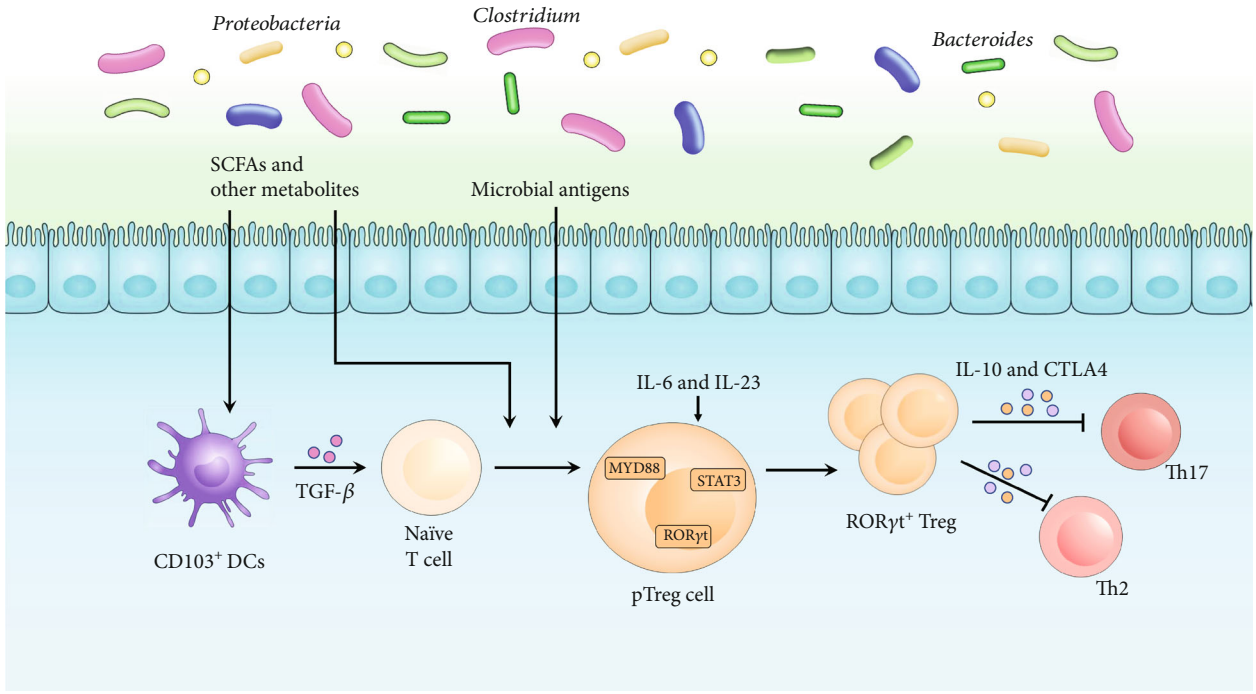

Figure 2: The composition of gut microbiota influences the expression of RORγt+ Treg to foster immune tolerance.

Foxp3$^+$CD4$^+$Treg cells are found in various organs of the body, accounting for about 10% of the total number of CD4$^+$ T cells [7]. In the intestinal lamina propria, they account for a much higher proportion: more than 30% of CD4$^+$ T cells in the colonic lamina propria and about 20% of the small intestinal lamina propria [7]. Intestinal Foxp3$^+$ Treg cells regulate mucosal immune responses at various cellular levels through multiple molecular mechanisms [32, 48]. They constitutively express IL-10, CTLA4 [49], TGFβ [50], and inducible T-cell costimulatory factor (ICOS) and IL-35 [51, 52] and maintain control of dietary components and gut microbiota immune tolerance.

3.2. Expression Regulation of Intestinal RORγt$^+$ Treg. Treg cells further obtain function-specific features, such as expression of RAR-RORγt, to adjust to the gut environment [7, 53]. RORγt is expressed by 20-30% Foxp3$^+$ T cells in the lamella propria (LP) of the intestine and about 10% Foxp3$^+$ T cells in the spleen and peripheral lymph nodes [9, 54]. Transcriptional activator 3 (STAT3), a signal transduction molecule activated by interleukin 6 (IL-6) and IL-23, mediates RORγt expression [7, 28], which enhances the suppressor function of colonic Tregs [9]. RORγt$^+$ Treg cells express high levels of IL-10 [52], interferon regulatory factor 4 (IRF4) [11], and CTLA4 [49], moreover promote to the inhibition of spontaneous Th2 response and control of the immune homeostasis of symbiotic microbes.

3.3. Regulation of Food Allergy by RORγt$^+$ Treg Cells. Induction of RORγt$^+$ Treg cells in the small intestine draining lymph nodes is critical for establishing intestinal luminal antigen tolerance [55]. It has been reported that RORγt$^+$ Treg cells are markedly reduced in peripheral lymph nodes of human subjects with FA [56]. Moreover, Th2-like reprogrammed Treg cells were unable to inhibit allergen-specific T-cell responses and emergence, and the secreted IL-4 promotes mast cell expansion and allergen-specific IgE responses, which accelerate the progression of the disease [57].

The mechanism by which the symbiotic microbiome generates protective RORγt$^+$ Treg cells is through a Treg cell-specific common upstream pathway involved in the primary response 88 of myeloid differentiation (MyD88). This pathway establishes the MyD88-RORγt signaling axis in incipient Treg cells in the gut, which intermediates tolerance induction in FA symbionts [58]. Previous studies have shown that MyD88 signaling promoted the production of iTreg cells at the mucosal interface, coordinate the regulation of intestinal mucosal cells and humoral adaptive immune responses, and facilitate tolerance [59] (Figure 2). Additionally, it can promote IgA immunity to the commensal microbiota, maintain a healthy commensal state by modulating follicular regulatory T cells (Tfr) and follicular helper T cells (Tfh) differentiation in Peyer's patches [59], and suppress mucosal immune response caused by dysregulation of microbiome.

4. Gut Microbiota Promotes Immune Tolerance by Regulating RORγt$^+$ Treg Cells

4.1. Gut Microbiota Enhances Immune Tolerance by Inducing Treg Cells. It is well known that the mammalian colon contains a dense community of symbiotic microbes that has a profound influence on immune system maturation and tolerance acquisition [59, 60]. There is now growing evidence that the gut microbiome plays a key role in

early host immune development and can alter the risk of allergic disease [61]. This part of the function is achieved by inducing the production of Treg cells. Treg cells inhibit microbial-induced intestinal inflammation, while the $CD4^+$ T cell compartment is formed by the existence of specific microbiome [60]. Treg cell response induced by microbiome colonization is the basic internal mechanism to induce and maintain the symbiosis of host intestinal microbial T cells.

Previous studies have shown that gut microbiota colonization in germ-free mice results in an extension of Treg cell populations in the gut lamina propria [60, 62]. Colonization of *Clostridium* and *Bacteroides* (two important members of the mammalian gut microbiome) leads to the induction and maintenance of colonic Treg cells [63]. Atarashi et al. [62] showed that oral intervention in germ-free mice with a mixture of 46 strains of conventional murine derived *Clostridium* resulted in strong induction of colonic Treg cells. Round et al. [63] found that the immunomodulatory molecule polysaccharide A (PSA) of *Bifidobacterium fragilis* mediated the conversion of $CD4^+$ T cells into $Foxp3^+$ Treg cells, which produced IL-10 during symbiotic colonization. IL-10 is mainly derived from $Foxp3^+$ Treg cells [9, 60], and the main role of IL-10 is to inhibit the response of Th2 cells [64]. The forming of intestinal homeostasis during colonization relies on IL-10, and studies have shown that blocking IL-10R during colonization may lead to immune bias [56]. In contrast, Th2-mediated inflammatory responses were exacerbated in Tregs-deficient mouse models [65]. Furthermore, animals with food allergy model also showed enhanced Th2 cell response, inhibited Treg cell expansion, and significantly increased Th17/Treg ratio [66]. These findings confirm that early gut microbiota changes can affect the proliferation and induction of Treg cells and thus the forming of gut homeostasis.

4.2. Gut Microbiota Metabolites Short-Chain Fatty Acids (SCFAs) Protect against Food Allergy. Dietary fiber is fermented in the colon by anaerobic bacteria into short chain fatty acids (SCFA), mainly acetate, butyrate, and propionate. In a model of enteropathogenic infection, acetate produced by protective *Bifidobacterium* promotes epithelial integrity, whereas SCFA enhances intestinal integrity in vitro [67]. Tan et al. [68] showed that high-fiber feeding increased the release of short-chain fatty acids (SCFA), especially acetic and butyrate, and protected against food allergy by enhancing retinal dehydrogenase activity in $CD103^+$DC. This protection depends on vitamin A in the diet. This intervention also promoted IgA production and enhanced the response of T-follicle helper cells and mucosal germinal centers. Mice lacking SCFA receptors GPR43 or GPR109A showed increased food allergy and decreased $CD103^+$DC [69]. Thus, SCFA improves oral tolerance and prevents food allergies in mice.

4.3. SCFAs Enhanced the Expression of RORγt$^+$ Treg Cells. The generation of RORγt$^+$ Tregs was dependent on dendritic cells (DCs) and major histocompatibility complex (MHC) class II [28] and expresses high levels of CTLA-4 and IL-10 to suppress Th2 responses [49, 64]. Microbiota induces the production of intestinal dendritic cells and regulates the proportion and function of colonic Tregs through short-chain fatty acids (SCFA) and food antigens [29, 70]. Microbiome derivatives are transported from the lumen to draining lymph nodes through $CD103^+$ DC and generate RORγt$^+$ Treg cells [71].

Studies have shown that supplementation with SCFA or propionate alone significantly raised the expression of Foxp3 and IL-10. The data of Smith et al. [65] suggest that SCFA may have beneficial effects on SPF mice by increasing the production of $Foxp3^+$IL-10, Treg, and altering Treg GPR15 expression. G-coupled protein receptor (GPR) 43 (Ffar2 is the gene encoding GPR43) binds to SCFA and mediates the resolution of inflammatory responses through its expression on innate immune cells [72]. Xu et al. [73] reported that the host regulates tolerance to potential pathogens by inducing RORγt$^+$ $Foxp3^+$ Treg, which optionally inhibit Th17 cells in a function that rely on the transcription factor c-Maf. Inactivation of c-Maf in the Treg compartment impairs bacterial-specific iTreg induction and function, involving IL-10 generation, leading to accumulation of Th17 cells and spontaneous colitis.

Britton et al. [74] found that transferring the IBD microbiome into germ-free mice raised the number of Th17 and Th2 cells and reduced the number of RORγt$^+$ Treg cells compared with the microbiome from healthy donors. This implies that the induction of RORγt$^+$ Treg cells depends on the intestinal microbiota and has a strong inhibitory factor and a steady phenotype. Studies have shown that mice selectively deficient in RORγt in Treg cells are more susceptible to intestinal inflammation, and microbial interventions that induce RORγt$^+$ Treg cells can protect mice from colitis [53, 72].

Along these lines, RORγt$^+$ Tregs may be important factors in limiting microbial dysbiosis and intestinal inflammation [75], and the production of RORγt$^+$ Tregs depends on the presence of gut microbes, including *Clostridium*, and other members of *Firmicutes*, *Bacteroidetes*, and *Proteobacteria* support their differentiation [53, 58].

5. Gut Microbiota Protects against Food Allergy by Modulating RORγt$^+$ Treg-Mediated Immune Tolerance

5.1. Gut Microbiota Maintain Immune Tolerance by Driving RORγt$^+$ Treg Cell Expression through the MYD88 Pathway. Myeloid differentiation primary reactive protein 88 (MyD88) is an intracellular adaptor protein that coordinates proinflammatory signaling cascades [76]. Except for its part in innate immune cells, MyD88 also plays a significant role in T cell responses [77]. Several studies have demonstrated the important roles of MyD88 in T cells. For example, T cell expression of MyD88 is essential for *Toxoplasma gondii* resistance [78], the emergence of MyD88-dependent signaling pathway in $CD4^+$ T cells has been shown to improve humoral immune response [79], and the development of inflammatory bowel disease requires MyD88 to act as a T cell effector [80]. TLR agonists signal through MyD88 to increase T cell activation and cytokine generation [81, 82]. Abdel-Gadir et al. [58] reported that specific deletion of

the TLR adapter MyD88 in Treg cells led to a deficiency of intestinal Treg cells, an increase in Th17 cells, and a raise in IL-17-dependent inflammatory response. The promotion of Treg cell formation by gut microbiota includes TLR signal transduction, which was demonstrated by the double deficiency of TLR connector molecules MyD88 and TRIF in germ-free mice during Schaedler flora colonization, and the inability to dilate colonic lamina Treg cells [59]. Furthermore, MyD88 signaling in Treg cells supports the antimicrobial IgA antibody response through a STAT3-dependent mechanism, thereby inhibiting the overgrowth of segmental filamentous bacteria (SFB) and the response of Th17 cells to promote healthy symbiosis [83]. In conclusion, MyD88 in Treg cells combines various signals from the gut microbiota to enhance the function of mucosal Treg cells and symbiosis by regulating the antimicrobial IgA response [84]. The loss of MyD88 or Rorc in Treg cells counteracts the protective effects of bacterial therapy. Therefore, the symbiote activates the MyD88/ROR-γt pathway in newborn Treg cells to prevent FA. Ecological imbalance in FA disrupts the MyD88-ROR-γt regulatory axis, resulting in decreased IgA and increased IgE responses to the gut microbiota, which is consistent with Treg cell-specific deletion of Rorc [58].

5.2. Supplementation of Probiotics Promotes Early Colonization of the Gut Microbiota and Enhances Immune Tolerance. Changes in members of the gut microbiota predispose children to food allergies, possibly through changing Toll-like receptor signaling and intestinal epithelial cell integrity [83]. Colonizing the gut of germ-free mice with *Clostridium*-containing microbiota prevents food allergies by activating innate lymphocytes, producing IL-22, and enhancing intestinal permeability [34, 62]. Probiotics are considered living bacteria that inhabit the gastrointestinal tract, and their number and function are related to the health benefits of the host [85]. Restoring a healthy gut microbiome through supplementation of probiotics and prebiotics is a potential pathway for inducing intestinal tolerance [86]. In the colon, anaerobic bacteria ferment dietary fiber to produce short-chain fatty acids (SCFA), mainly represented by acetate, butyrate, and propionate. Research by Tan et al. [68] found that a high-fiber dietary intervention in mice improved the microecological balance of the gut and increased the production of SCFA, particularly acetate and butyrate. High-fiber dietary interventions enhance oral tolerance and prevent food allergies by improving retinal dehydrogenase vitality in $CD103^+$ DCs [68]. Many probiotic species are capable of stimulating the production of secretory IgA by antigen-bound B cells, thereby limiting their entry into epithelial cells [87]. Probiotics increase the cytotoxic potentiality of NK cells and the phagocytic capacity of macrophages and have antiviral performance. Macrophages are very important for initiating the acquired immune response, which can protect against food allergy to a certain extent. In the study by Schiavi et al. [88], oral treatment with a probiotic mixture was reported to be beneficial to redirect allergen-specific Th2-polarized immune responses to Th1-T regulatory responses and prevent allergen-induced allergic reactions. Studies have shown that raising serum IgE levels lead to elevated mast cell surface binding IgE levels, and germ-free mice exhibit increased antigen-induced oral allergic reactions compared to normal mice [89], suggesting that immune response disorders such as food allergies may be extremely relying on the acquisition of sufficient bacterial consortia at an early stage. It has been shown that to set a baseline immunomodulatory state of life, it is necessary to be exposed to multiple microbiota during crucial time windows of early life [90].

6. Conclusions and Future Directions

In the present, a large number of studies have confirmed that food allergy is closely correlated with the structural changes of the gut microbiota. And one of the mechanisms could be that the gut microbiota promotes the establishment of immune tolerance by regulating the expression of Treg and RORγt$^+$ Treg to prevent food allergy. The gut microbiota and its metabolites activate the MyD88 signaling pathway through TLR signaling and STAT3-dependent mechanisms to enhance the expression of mucosal Tregs and RORγt$^+$ Treg. RORγt$^+$ Treg cells express high levels of IL-10 and CTLA4, inhibit Th2 cellular responses, maintain intestinal tolerance, and protect the body from intestinal inflammation. Conversely, the MyD88-ROR-γt regulatory axis is disrupted in dysbiosis, exacerbating intestinal inflammation and allergic diseases. However, it was unclear whether allergies to individual foods exhibit the obvious and overlapping regulatory mechanisms of RORγt$^+$ Treg cells in all food allergic disorders.

More supporting data suggest that probiotics play a protective role against colonization of the gut microbiota, for example, by stimulating epithelial cells to increase mucosal integrity, increase mucin secretion and activity of NK cells, and increase stimulation of IgA production [34, 86, 90, 91]. By supplementing probiotics or prebiotics to promote the early colonization of gut microbiota and enhance immune tolerance, it provides a new idea for the prevention of food allergy in newborns.

Conflicts of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Authors' Contributions

Xixi Ning and Ming Li conceived and designed this review. Qianqian Ning wrote the first version of the manuscript. Zengjie Lei and Binqi Rui collated the research literatures. Yuyuan Li and Ming Li revised and finalized the manuscript. All authors read and approved the final version of the manuscript.

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