Review Article
The Roles and Mechanisms of Gut Microbiota in Food Allergy

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Recent research reveals that the increasing prevalence of food allergies (FA) is due in part to changes in the commensal microbiome. Studies in humans have shown that compared with healthy controls, individuals have distinct gut microbiomes during the onset and progression of FA. 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. New therapeutic and preventive approaches to altering the gut microbiota using diet adjustments, probiotics, prebiotics, synbiotics, postbiotics, fecal microbiota transplantation, and Chinese medicine have been developed towards FA. Herein, we summarized the latest evidence on the gut microbiota profiles and functions associated with FA, oral tolerance mechanisms, and gut microbiota-targeted therapeutic strategies for FA.

1. Introduction
Food allergy (FA) 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 [1]. Cow’s milk, eggs, peanuts, soy, seafood, and shellfish are the most typical food allergens [2, 3]. Currently, FA is becoming a significant health issue that affects more than 220 million people globally [4, 5]. In developed countries, 5%–10% of the population has FA, including an estimated 32 million Americans [6]. FA was once considered rare in developing countries, but recent epidemiological investigations have revealed a rise in incidence [7]. The prevalence of challenge-proven FA among infants aged 0–24 months has been reported to have increased significantly from 3.5% to 7.7% in China [8, 9]. In addition, the prevalence of allergies in the elderly was reported from 5% to 10% and appears to increase [10]. Multiple organs and systems, including the skin, gastrointestinal, respiratory, cardiovascular, and nervous systems, may be affected by the clinical features of FA [11, 12]. Correspondingly, the severity of clinical symptoms ranges from mild to life-threatening, such as urticaria, vomiting, and airway inflammation. Anaphylaxis, its most extreme manifestation, is a severe allergic reaction that impacts numerous organ systems and can cause hypovolemic shock [13]. Although the number of patients is increasing yearly, there was no definitive treatment for FA until 2020, when the first medicine for peanut allergy was approved. However, for other food allergies, the standard care remains strict avoidance of allergens and adrenaline treatment for systemic reactions...
brought on by food allergens [6]. Therefore, the development of efficient therapeutic interventions requires a deeper comprehension of FA pathogenesis.

Genetic factors alone cannot account for the dramatic rise in FA prevalence over the past 100 years, clearly indicating that environmental factors also play a substantial role in susceptibility [14]. In 1989, the “hygiene hypothesis” initially linked the environmental factor to FA [15]. Additionally, mounting evidence points to the importance of gut bacteria in the control of allergic hyperreactivity, and the hygiene hypothesis has been extended to the “old friends” hypothesis [16]. Mechanistically, FA is the breakdown of immunologic and clinical tolerance to food antigens. Intimate interactions between the intestinal epithelium, the immune system, and the gut’s resident microbiome are essential for the development and maintenance of oral tolerance. The gut microbiome, called as “forgotten organ,” is a collection of gut microbiota and its genetic material that supports human life and health [17]. Growing evidence has shown that a healthy gut microbiota contributes to protect against FA, whereas disruption of the gut homeostasis (dysbiosis) affects oral tolerance and confers susceptibility to FA [18, 19]. Studies using advanced molecular techniques, including 16S rRNA sequencing and shotgun metagenomic sequencing, revealed that the gut microbiota of children with FA differs from that of healthy children in terms of microbial diversity and composition [18, 20]. Additionally, the gut microbiome of young children with milk allergies that resolved by the age of 8 years was distinct from that of infants with persistent milk allergies [21]. The initial intestinal microbiota structure and composition are to blame for the differences in the gut microbiota’s susceptibility to dextran sulfate sodium therapy, according to a new mouse model study [22]. In animal models and clinical trials, reintroducing specific commensal bacteria, including Clostridia, resulted in the prevention or treatment of allergy [23]. Additionally, the feces of FA patients had lower quantities of short-chain fatty acids (SCFAs), particularly butyrate, which are byproducts of the gut microbiota’s fermentation of dietary fiber [24–26]. In recent years, subsequent studies have shown that SCFAs exert multiple protective effects against FA [27]. All these provide a basis for developing innovative strategies for FA prevention and treatment targeting the gut microbiota.

In this review, we will highlight the most recent development in our understanding of how the gut microbiota contributes to FA. Furthermore, we focused on the gut microbiota’s potential role as a target for innovative strategies against FA.

2. Gut Microbiome Features and Functions in Food Allergy

We have made significant progress in understanding the composition and function of the gut microbiota in FA, thanks to the advancements in genomic DNA sequencing technologies. Early studies that focused on the gut microbiota in people with FA were culture-based, which had the drawback of limiting their focus to specific bacterial groups and individuals because most the bacteria could not be cultured. Our understanding of the relationships between the gut microbiota and human health or disease is also expanding owing to transcriptomics, proteomics, and metabolomics.

Studies based on next-generation sequencing technology have revealed that individuals without FA and those with FA had significantly different gut microbiota structures, and gut dysbiosis may precede the onset of FA. In 2014, our group studied the differences between children with FA and healthy children and found that in children with immunoglobulin E- (IgE-) mediated FA, Clostridium sensu stricto and Anaerobacter increased, while Bacteroides and Clostridium XVIII decreased [28]. The gut microbiota of FA patients differed significantly from age-matched controls in terms of both α-diversity and β-diversity, according to a new large-scale study that included 233 patients with FA and 58 non-allergic controls [26]. Prevotella copri was the most overrepresented species in the group of healthy controls, but the allergic group had high levels of Collinsella aerofaciens, Dorea formicigenerans, unclassified Methanobrevibacter, Blautia obeum, and Coprococcus catus. With an area under the curve of 0.9, these microbial differences could be used to separate FA patients from healthy controls. Moreover, the authors found that P. copri was connected with all three SCFAs and that the levels of SCFAs were lower in FA patients than in controls. A cohort study of genetically identical twins with comparable childhood lives provided stronger evidence that the gut microbiota was responsible for the striking increasing in FA prevalence [29]. Between the healthy and allergic twins, there were 64 operational taxonomic units (OTUs) that were significantly different; the healthy twins had a marked increase in the Clostridia class. The abundances of Citrobacter, Oscillospira, Lactococcus, and Dorea were found to be lower in stool collected at ages 3-6 months in children who had FA by age 3 years in a prospective study with a cohort of 225 children from the United States; this finding suggests that the gut microbiota may play a causal role in the onset of FA [30]. Using the shotgun metagenomics approach, De Filippis et al. were the first to describe the specific gut microbiome features in children with FA or respiratory allergies; this finding demonstrated that the gut microbiome of allergic patients was different from that of healthy controls, with higher abundances of Faecalibacterium prausnitzii and Ruminococcus gnavus and lower levels of Bifidobacterium longum, Bacteroides dorei, B. vulgatus and several other fiber-degrading taxa, and R. gnavus may be involved in the pathogenesis of allergic disease [31]. Earlier observational human cohort studies have been reviewed elsewhere [20, 32].

Findings from murine models also suggest a close connection between gut microbiota and FA. Germ-free mice completely lacking a normal gut microbiota or mice treated with antibiotics to reduce the bacteria load in the intestine showed a predisposition to FA. This can be fixed by reintroducing a diverse microbial community early in life, but not later. The Il4raF709 mouse, a model for FA-prone mice with an interleukin- (IL-) 4 receptor gain of function mutation, has a different gut microbiota than wild-type mice [33]. Bacterial families such as Lachnospiraceae, Lactobacillaceae, Rikenellaceae, and Porphyromonadaceae were overrepresented in the
Il4raF709 mice. Moreover, the Il4raF709 mice’s transfer of their gut microbiota to germ-free mice appeared to transfer their vulnerability to disease, and this was the first experimental model to demonstrate that FA susceptibility could be transmitted by the gut microbiota. Consistent with this report, “humanized mouse models” were developed by Feehley et al. to investigate the gut microbiota’s potential role in FA suppression [34]. Mice that received fecal microbiota transplantation (FMT) from healthy infants were protected against milk allergy, but mice who received FMT from infants who were allergic to cow’s milk suffered severe anaphylactic reactions to the allergen. Anaerostipes caccae, a clostridial species, was closely associated with the ileum’s regulatory gene expression, which prevented an allergic response to food. Overall, a low abundance of SCFA-producing bacteria, such Clostridium, may contribute to the development of FA, despite the fact that no particular microbial genera or species are consistently linked to FA [14, 26, 28, 29, 35, 36].

The metabolites produced by the gut microbiota, such as SCFAs, tryptophan metabolites, and secondary bile acids, have favorable effects on FA. The primary byproducts of commensal bacteria’s fermentation of complex and nondigestible carbohydrates, like dietary fibers, are SCFAs, which include acetate, propionate, and butyrate. Mice raised in a germ-free environment do not create SCFAs due to a diminished gut microbiota; however, supplementing with acetate greatly reduced illness indicators. Allergies are brought on by gut microbial dysbiosis, which decreases SCFA levels. A growing body of research suggests that raising the levels of SCFAs can reduce the illness state and tendency for allergic dermatitis that results from their deficiency. For example, Roduit et al. have identified a substantial correlation between SCFA levels and infants’ health [20]. They demonstrated that between the ages of 3 and 6 years, children who had the greatest levels of butyrate and propionate in their early lives had significantly less atopic sensitization and a decreased risk of developing asthma. Additionally, some probiotics may promote oral tolerance and provide protection from FA, which is partly due to the SCFAs. In one trial, extensively hydrolyzed casein formula and Lactobacillus rhamnosus GG (LGG) were given to newborns to assist them develop tolerance to cow’s milk allergen, in part by increasing the number of bacterial strains that produce butyrate [24].

3. The Mechanisms of Gut Microbiota in Oral Tolerance and Food Allergy

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. Because the immune system can distinguish between harmful and harmless environmental antigens, healthy individuals typically maintain prolonged resistance to common dietary antigens. The stimulation of Treg cells is the main mechanism controlling immune tolerance to dietary antigens [43]. Conversely, FA 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 [14]. The interplay between immune cells and the gut microbiota helps to maintain the balance between immune tolerance and FA. The role of the commensal microbiome in promoting tolerance and the connection between intestinal dysbiosis and FA 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 [37, 44–46].

3.1. Tolerance. Under homeostatic states, food antigens within the gastrointestinal lumen translocate across the gut epithelium and into the intestinal mucosa through multiple mechanisms, including passage through gaps between epithelial cells, transport through epithelial cells, and uptake by specialized microfold (M) cells located on the Peyer patches and goblet cells [11, 47, 48]. The mucosal antigen-presenting cells (APCs), such as dendritic cells (DCs) and macrophages, are then sampled with these delivered antigens. By extending dendrites across the epithelial cells, CX3C-Chemokine receptor 1 (CX3CR1) macrophages can collect antigens directly from the intestinal lumen and pass them to CD103+ DCs [49]. Antigen-loaded DCs move to the mesenteric lymph nodes (MLNs), where they release transforming growth factor-β (TGF-β) in the presence of the vitamin A metabolite retinoic acid (RA), which causes naïve T cells to differentiate into antigen-specific forkhead box P3 (Foxp3+) Treg cells [50]. These Treg cells then return

[continued]
to the gut and continue to expand under the influence of IL-10 generated by local CX3CR1+ macrophages [51]. Treg cells regulate B cell antibody isotype switching to IgA via production of TGF-β. IgA is transported into the mucosal lumen after passing through the epithelial barrier and keeps luminal food antigens out (Figure 1) [52].

3.2. Tolerance Breakdown. The tolerance breakdown is characterized by the transformation of CD103+ DCs from inducing Treg cells to proallergic Th2 effector cells. This switch may be brought on by a number of causes, including damage to the intestinal epithelium and exposure to certain pathogen-associated molecular patterns (PAMPs). Studies have demonstrated that the ability of DCs to stimulate Th2 cells may be improved by activating PAMP receptors such as TLR2, TLR5, TLR7, and TLR8 [53, 54]. Epithelial damage promotes the release of cytokines generated by the epithelium, including IL-25, IL-33, and thymic stromal lymphopoietin (TSLP), which induces and expands Th2 cells [55]. These Th2 cells generate significant levels of IL-4, trigger B cell IgE switching, support mast cell survival, and, through an autocrine loop, encourage the growth of Th2 cells. Tolerogenic Treg cells are rendered inactive by IL-4 and transformed into pathogenic Th2-like cells [56]. Moreover, the cytokines produced by the gut epithelium promote the growth of ILC2s, which secrete IL-4 and IL-13 that prevent Treg cell activity [57] (Figure 1).

3.3. Commensal Bacteria Mediate Immune Tolerance. Increasing evidence indicates that gut commensal bacteria, through a variety of pathways, play a critical role in modulating immune tolerance to dietary antigens (Figure 2). The induction of Treg cells stands out among these. In particular, the establishment of tolerance to dietary antigens is not fully understood, there is strong evidence to suggest that bacterial metabolites such SCFAs play a crucial role in maintaining epithelial barrier function and immune tolerance in the gut [37, 59].
3.3.1. Treg Differentiation. According to the paradigmatic view, the main mechanism regulating oral tolerance to dietary antigens is the induction of food antigen-specific Treg cells. Several studies have reported that specific gut microbes can promote the differentiation of Tregs through interactions of microbial molecules with corresponding pattern recognition receptors (PRRs), such as TLRs. Microbiota-produced metabolites are also involved in shaping the differentiation of Tregs, including SCFAs, tryptophan metabolites, and bile acid metabolites.

Gut microbiota promotes the induction of Treg cells by increasing IL-10 production. IL-10, a critical immunoregulatory cytokine in the process of Treg induction, requires the intact microbiota. Kim et al. demonstrated that antibiotic-treated mice’s CX3CR1⁺ mononuclear phagocytes were unable to generate IL-10, favoring proinflammatory Th1 cell responses and suppressing anti-inflammatory Treg cell responses. But when microbes were reintroduced, they resumed their IL-10-expressing activity, limited the growth of T effector cells, and stimulated the proliferation of Treg cells [60]. Furthermore, Sun et al. have shown that Bifidobacterium treatment could improve Treg activity by encouraging an IL-10/IL-10Ra self-stimulatory loop in mice [61].

Moreover, gut microbiota promotes Foxp3⁺ Treg expansion by increasing the level of IL-2. Zhou et al. showed that the intact microbiota drove intestinal macrophages to produce IL-1β through a myeloid differentiation primary response 88- (MyD88-) and Nod2-dependent mechanism, which then facilitated ILC3 to produce IL-2 [62]. Furthermore, granulocyte-macrophage colony-stimulating factor (GM-CSF), a key cytokine for the induction of mucosal Treg cells, can be induced by IL-1β in ILC3 cells [63]. This interaction is disturbed, which drastically lowers the number of mucosal Tregs and impairs oral tolerance to food antigens.

Commensal microbes influence RA and TGF-β levels, which affects the abundance of Treg numbers. TGF-β is essential for the generation of intestinal Tregs. By cleaving the latency-associated peptide bound to the inactive form of TGF-β, the αvβ8 integrin produced by DC activates this growth factor. And gut microbiota through TLR signaling influences β8 expression in part [64]. Similar to TGF-β, RA is essential for maintaining tolerance in the intestine by inducing Foxp3⁺ Treg cells. Retinal dehydrogenase enzyme (RALDH) is an important enzyme in CD103⁺ DC synthesis of RA, while Aldh1a2 is its main isoform. Studies have revealed that the expression of Aldh1a2 might be modulated by several microbial stimuli, such as MyD88-dependent TLR2 signals and the Wnt/β-catenin pathway [65]. Another study showed that acetate, a member of microbiota metabolite SCFAs, could induce DC to express Aldh1a2 [66]. In addition, Schlierfink et al. found that butyrate, in contrast to other SCFAs, could induce Aldh1a1 or Aldh1a3 expression via histone deacetylase 3 inhibition and thereby support epithelial RA production [67].
Tryptophan metabolism, which is triggered by the enzyme indoleamine 2,3-dioxygenase (IDO), has recently been recognized as a key player in immune tolerance to dietary antigens. The induction of Treg cells is the primary mechanism by which the IDO pathway induces tolerance [68]. The formation of Tregs and the development of tolerance, however, are hampered by blocking IDO expression in vivo [69]. Moreover, the tryptophan metabolite kynurenine induces naïve CD4⁺ T cell differentiation into immunosuppressive Foxp3⁺ Tregs in vitro [40]. In comparison to healthy controls or children with FA who had developed tolerance, those with FA showed lower serum kynurenine/tryptophan ratios [38]. Furthermore, compared to specific pathogen-free mice, tryptophan metabolism is reduced in germ-free and antibiotic-treated mice. However, kynurenine metabolite levels were restored following the reintroduction of gut microbes. Together, these suggest that the gut microbiota is crucial to the kynurenine pathway [70]. Mechanically, a key factor in initiating tryptophan metabolism has been found as TLR stimulation by microbial components.

SCFAs are critical for the development of Treg cells. Some groups have discovered a positive link between the quantity of colonic Treg cells and the concentration of luminal SCFAs using a number of quantitative investigations [71]. Studies suggested that butyrate facilitated the extrathymic production of Treg cells with the help of a Foxp3 enhancer known as conserved noncoding sequence 1 (CNS1), while propionate promoted peripheral Treg differentiation [42, 71]. Different G protein-coupled receptors (GPCRs) expressed on Tregs and innate immune cells modulate the effects of SCFAs on Treg cells, and these GPCRs were dependent on the presence of the gut microbiota. Using GPR43-deficient mice directly results in reduced colonic Treg numbers in vivo [72]. GPR109a specifically binds butyrate and promotes IL-10 and RALDH production by macrophage and DC, leading to Treg generation [73]. In a peanut allergy study, the authors found that high-fiber effects rely on the interactions between acetate and butyrate and their receptors, epithelium GPR43 and immune cell GPR109a, which promote higher Treg cell differentiation [74]. Beyond modulating Treg differentiation, pentanoate and butyrate also induce IL-10 production by B cells, thereby promoting the differentiation of regulatory B cells [75].

The development of RORγ⁺ Treg cells is controlled by the gut microbiota, which influences oral tolerance. As a key Treg member, RORγ⁺ Tregs are essential for the induction and maintenance of intestinal tolerance and homeostasis [76]. Its maintenance depends on the gut microbiota, and they are sensitive to microbiota shifts. A specific consortium of six Clostridiales-type strains used in microbiota therapy stimulates a MyD88-dependent pathway in developing Treg cells, resulting in the development of FA-suppressing RORγ⁺ Treg cells, which are absent in FA patients [44]. In addition, two recent studies found that the generation of colonic Foxp3⁺ Treg cells that express the transcriptional factor RORγt was controlled by bacterial metabolism of bile acids (BA) [41, 42]. This Treg cell type was significantly reduced in gut symbionts following genetic ablation of the BA metabolic pathway.

3.3.2. Basophils. Commensal bacteria have been demonstrated to influence the amount of allergy effector cells. For example, commensal bacteria may be a regulator of circulating basophil populations. Antibiotic-treated or germ-free mice have higher serum IgE levels as well as more circulating basophils [77]. Furthermore, different from control mice, Hill and Artis also found that antibiotic treatment could not increase circulating basophils in anti-IgE-treated mice. The process was investigated, and it was discovered that the signals produced by commensal bacteria act through a B cell-intrinsic, MyD88-dependent signaling pathway, restricting serum IgE levels, and circulating basophil populations [78]. As mentioned earlier, the body can develop tolerance to food antigens by producing IgA. Interestingly, a significant portion of the commensal microbiota is IgA-coated, and IgA is mainly produced in the small intestine, although the detailed mechanism of IgA in food tolerance is not clear [79, 80]. In addition, Wu et al. have demonstrated that acetate stimulates GPR43-mediated B cell IgA class switching and IgA secretion [66].

3.3.3. Epithelial Barrier Integrity. Another important way through which the gut microbiota promotes oral tolerance is epithelial barrier integrity modulation. The barrier integrity is the body’s first line of defense against food allergens. Our knowledge from human and murine studies indicates that commensal bacteria play vital roles in maintaining epithelial barrier integrity through itself and/or its metabolites such as SCFAs and indole derivatives [37].

An increasing body of research indicates that the gut microbiota promote mucus secretion and mucin formation, which in turn helps to maintain the integrity of the epithelial barrier. Maintaining barrier integrity and avoiding food and bacterial antigen leakage into the lumen are both facilitated by a dense mucus layer. In an earlier study, the authors found that SCFAs containing acetate could induce the expression of mucin 2 (MUC-2) in intestinal epithelial cells [81]. A further research revealed that in addition to its physical barrier function, MUC-2 might imprint tolerogenic features in DCs by promoting the production of IL-10 and TGF-β1 [82]. Additionally, Wrzosek et al. also found that germ-free mice supplemented with B. thetaiotaomicron, a producer of acetate, showed enhanced mucus secretion [83]. Moreover, butyrate and other SCFAs have strong effects on tight junctions and mucin production [84].

In addition, gut microbiota also promotes epithelial barrier integrity via inducing IL-22 production by ILC3. It has been determined that IL-22 is a crucial cytokine that manipulates barrier functions at the mucosal surface. Mechanically, the metabolite-sensing receptor free fatty acid receptor 2 (FFAR2, also named as GPR43) is requisite for this activity. Chun et al. showed that deletion of FFAR2 in ILC3s significantly decreased the production of IL-22, which resulted in poor intestinal epithelial function characterized by altered mucus-associated proteins and antimicrobial peptides as well as increased susceptibility to bacterial infection and colonic damage [85]. In a previous research, Stefka et al. also demonstrated that early innate IL-22 production by RORγt ILCs and T cells in response to Clostridia regulates...
intestinal epithelial permeability, which in turn lessens the ability of food allergen to enter the bloodstream and contributes to FA protection [45].

Moreover, the role of IL-17 in maintaining the integrity of mucosal epithelial barriers has been well established. Mechanically, IL-17 regulates the tight junction protein occludin through an Act-1 signaling pathway in epithelial cells, thereby limiting excessive permeability and maintaining gut barrier integrity [86, 87]. Th17 cells, as a main IL-17 producer, are found in the lamina propria of the small intestine, and their generation is regulated by specific microbes. Segmented filamentous bacteria may control the development of Th17 cells in rodents [88]. In humans, Tan et al. have identified that the symbiont microbe B. adolescentis could induce Th17 cells [89]. In a longitudinal analysis of the Integrated Human Microbiome Project data, Zhou et al. found that alterations in the gut microbiota, as shown by a drastic decline in Clostridia occurred simultaneously with lower levels of IL-17 [90].

Indoles, a main microbial metabolite of tryptophan, have an established role in regulating epithelial barrier integrity [91, 92]. Indole administration resulted in increased expression of both tight and adherent junctions in intestinal epithelial cells, thus preventing leakage of luminal contents in germ-free mice [91]. Bansal et al. found that human enterocyte cells incubated with indole showed a significant increase in gene expression associated with mucosal barrier enhancement and mucin production [92]. Moreover, indole derivatives act as AHR ligands and can stimulate these receptors in immune cells to trigger the production of the barrier-protecting cytokine IL-22 [93]. In addition, as a ligand for the xenobiotic sensor PXR, indole 3-propionic acid (IPA) has been shown to regulate the integrity of the epithelial barrier in mice [94]. In a recent study, Dodd et al. highlighted this advantageous effect. They found that C. sporogenes fldC (a mutant strain that is incapable in synthesizing IPA) increased intestinal permeability in germ-free mice but not the wild-type C. sporogenes [95].

4. Gut Microbiota Manipulation for the Prevention and Treatment of Food Allergy

As mentioned above, dysbiosis of the gut microbiota is a key factor in the development of FA. Major progress has been achieved in our mechanistic understanding of FA, which provides an opportunity to develop novel therapeutic and preventive measures by manipulating the structure of gut microbiota. Diets, probiotics, prebiotics, symbiotics, postbiotics, FMT, and Chinese medicine represent candidate strategies to shape the gut microbiome for beneficial outcomes. Although many earlier studies have already been reviewed [23, 96–98], we will cite some newer reports in the following narrative.

4.1. Diets. Dietary intervention can rapidly affect the gut microbiota’s composition by introducing new species or changing the relative abundance of specific microbes in the community [99]. For instance, enterotypes dominated by Bacteroides and increased bile acid synthesis arise from meals high in animal protein and fat, which exerts a considerable selective pressure on the gut microbiota. Yet, a high-fiber diet encourages the development of dietary fiber-fermenting bacteria such Bifidobacterium and Lactobacillus, which results in an increase in SCFA levels and a suppression of Th2 differentiation [100, 101]. And each fiber is associated with fiber-dependent biochemical and microbial responses. For instance, long-chain inulin is associated with an increase in Bifidobacterium, whereas arabinobinoxyl consumption contributes to cholesterol reduction [102]. Dietary fibers are polymers made mostly from edible plant and animal parts as well as related carbohydrates that are neither digested nor absorbed in the human intestine. According to the existing evidence, the decline in dietary fiber is becoming one of the most significant factors in the increase in inflammatory diseases, such as inflammatory bowel disease, whereas a high-fiber diet contributes to protecting against allergy diseases. Mechanically, the beneficial effects mainly depend on its end products SCFAs metabolized by the gut microbes. As described in the mechanisms section, SCFAs have strong anti-inflammatory effects, both locally in the gut mucosa and beyond, inducing Treg cells and tolerogenic DCs. For instance, Tan et al. showed that high-fiber intake shielded mice from peanut allergy by reshaping the gut microbiota and increasing levels of SCFAs, particularly acetate and butyrate [74]. In addition, this protection depends on GPR43 and GRP109A, receptors of SCFAs, because mice lacking one of them showed exacerbated FA. Moreover, high-fiber diet also increased the tolerogenic CD103+ DC potency, which prompted a greater Treg cell differentiation. In a recent review, the dietary fiber pectin was reviewed in relation to potential uses in the management of allergies [103]. Pectin is a polysaccharide that comes from plants and is used as a food additive and gelling agent. Its consumption can change the Firmicutes to Bacteroidetes ratio, increase the amounts of SCFAs in serum and feces, and prevent the development of inflammation by impairing DC function. Even before birth, there is a growing interest in how maternal dietary fiber may influence immune development in the offspring and the subsequent risk of allergy. For example, the researchers found that increased maternal dietary fiber during pregnancy was associated with decreased infant wheeze in an observational study of 639 infant-mother pairs [104]. Dietary interventions have attracted great interest in the area of allergy prevention and treatment. They can rapidly shape the gut microbiota composition without any side effects. However, the majority of human randomized controlled trial (RCT) studies are short-term and demonstrate a quick return to baseline composition following the end of the intervention. Moreover, the mechanism is not well established. It is therefore necessary to do mechanistic study as well as studies on long-term diets that can induce stable changes in the microbiota.

4.2. Probiotics. Probiotics are termed as "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host." As these microorganisms can balance the intestinal microbiota, regulate epithelial barrier function, and modulate the immune system, preventing the
development of FA, previous studies have suggested that the administration of beneficial probiotics may be the key to reducing allergic symptoms and improving susceptibility to FA. Bifidobacterium and Lactobacillus are generally the two kinds of probiotics that are most frequently utilized, with LGG appearing to be the most extensively researched strain.

The evolution of knowledge demonstrates that probiotic administration in the first stage of life is more beneficial for the prevention and treatment of FA, because the microbiota is still developing in this period. Compared with atopic dermatitis, eczema, allergic rhinitis, etc., there are relatively few studies on probiotics in FA, and the most studied FA type appears to be cow milk allergy (CMA). For example, in a 3-year randomized controlled trial, Berni Canani et al. showed that extensively hydrolyzed casein formula (EHCF) combined with LGG significantly lowers the incidence of other allergic manifestations and accelerates the development of immune tolerance in children with IgE-mediated CMA [105]. Moreover, the administration of LGG dramatically raised the amounts of butyrate in the feces, which was previously established to be a factor in the development of oral tolerance [24]. In addition, LGG has also been studied in peanut allergy combined with peanut oral immunotherapy (OIT). Tang et al. have shown that children receiving the combination treatment had higher rates of desensitization to peanuts compared to placebo [106]. Recently, the effects of B. bifidum TMC3115 were explored in children with CMA. Jing et al. found that the B. bifidum TMC3115 administration for 6 months markedly reduced the level of serum-specific IgE, increased anti-inflammatory responses, and increased the proportion of probiotics and decreased the proportion of pathogens [107].

Using animal models, mainly in mice, different probiotics in isolation or mixtures were shown to have effects on FA prevention or treatment. According to Yang et al., treatment with B. infantis markedly reduced serum ovalbumin (OVA-) specific IgE and IgG1 levels as well as the release of Th2 cytokines in the spleen, which was dependent on Coprococcus and Rikenella [108]. Administration of C. butyricum CGMCC0313-1 significantly elevated slgA and Foxp3+ Treg cells in the spleen in mice with β-lactoglobulin (BLG) sensitivity and markedly reduced anaphylactic symptoms [109]. L. rhamnosus 2016SWU05.0601 has recently been demonstrated by Song et al. to modulate the expression of immune-related transcription factors and gut microbiota, consequently regulating the imbalance of Th1/Th2 and Treg/Th17 in OVA-sensitized mice [110]. Treatment with a probiotics mixture (L. lactis KF140, Pediococcus pentosaceus KF159, L. pentosus KF340, L. paracasei 698, and Bacillus amyoliquefaciens 26N) significantly suppressed the OVA-induced allergic symptoms, inhibited the release of IgE and Th2 cytokines, and promoted the development of Foxp3+ Tregs in mice [111]. Moreover, the combined effects of probiotic and OIT were also identified in mice. Kim et al. found that the simultaneous administration of L. casei variety rhamnosus and OIT has a synergic effect in the protection against anaphylaxis in egg-allergic mice [112].

It should be noted that the evidence relating to the use of probiotics in FA appears controversial. For instance, a sub-study of the ProPrems multicenter, double-blind, placebo-controlled randomized trial revealed that the incidence of FA was similar between the probiotic and placebo groups [113]. Adel-Patient et al. found that ECHF plus LGG administration was unable to prevent mice from developing cow’s milk allergy [114]. Besides, some systematic reviews and meta-analyses reveal that there is low certainty that probiotics can induce oral tolerance and moderate certainty that they can ameliorate the symptoms of children with CMA [115]. Nevertheless, probiotic supplementation during childhood may have little to no impact on preventing FA [116]. Moreover, the efficacy of probiotics is strain- and dose-dependent but also relies on its derived metabolites and postbiotics [117]. As a result, even in CMA, there is still no definitive recommendation on which strain to use, the dose, and the duration. It is also worth noting the impact of unique host microbiome features on the health-promoting probiotics. For example, probiotic gut mucosal colonization efficacy is a crucial factor affecting the effects of probiotics, which is associated with the host basal microbiome [118, 119]. A recent study showed that probiotics work better in individuals with a healthier gut microbiota composition than in others [120].

4.3. Prebiotics. In 2016, the concept of dietary prebiotic, “a substrate that is selectively utilized by host microorganisms and confers a health benefit,” was updated by the International Scientific Association for Probiotics and Prebiotics (ISAPP) [121]. Prebiotics bypass the upper gastrointestinal system, largely intact, and serve to affect microbiome growth and activity [122]. Dietary prebiotics enhance the growth of SCFA-producing bacteria and produce SCFAs such as acetate, propionate, and butyrate [123]. Human milk oligosaccharides (HMOs), fructans (such as inulin and fructo-oligosaccharides (FOS)), galactans (such as galacto-oligosaccharides (GOS)), and lactulose are currently recognized prebiotics [124]. However, the expanded definition of prebiotics may now cover noncarbohydrate substances, such as phytochemicals, polysaturated fatty acids (PUFA), conjugated linoleic acids (CLA), and phenolics. Over the past few decades, a multitude of health benefits have been described relating to dietary prebiotics. Therefore, it is no surprise that a multitude of research has linked prebiotics with improved gut health and may serve as important therapeutic or preventative agents to reduce the incidence of FA.

HMOs, the key constituents of human milk, are considered important early-life prebiotics [125, 126]. They are an assortment of physiologically and structurally diverse nondigestible sugars, which serve as a substrate for specific microbes, including species belonging to the Bifidobacterium and Lactobacillus genera. There are currently more than 200 HMOs in mother’s milk, and each mother’s HMO composition is different [125]. Current evidence indicates that HMOs play a significant role in attenuating allergic responses to CMA [127, 128]. Seppo et al. reported that 18-month-old infants who received lower levels of an HMO known as lacto-N-fucopentaose III (LNFP III)
(<60 μM) were at a higher risk of developing CMA compared to infants who received higher levels of LNFP III [129]. A recent RCT study confirmed that a whey-based EHF fortified with 2 HMOs (2′-fucosyllactose and lacto-N-neotetraose) met the clinical hypoallergenicity in infants with CMA [130].

Two meta-analyses showed significant effects on allergy mitigation following prebiotic supplementation. Supplementation with a GOS and FOS mixture (GOS/FOS 9:1 ratio) proved to significantly lower allergy incidences in infants at high risk of food allergy [131, 132]. Further, Zhang et al. found that GOS, FOS, and mannan-oligosaccharide could markedly desensitize shrimp tropomyosin-induced FA in mouse models [133]. Using a CMA mouse model, Li et al. have shown that HMO and its main component 2′-fucosyllactose (2′-FL) could effectively alleviate FA [134]. 2′-FL or HMO administration decreased the amount of BLG-induced serum-specific IgE and mast cell degranulation as well as the generation of inflammatory cytokines including TNF-α, IL-4, and IL-6. Another study further confirmed that 2′-FL or HMO decreased allergen-induced iNOS, NO, pro-inflammatory cytokines, and reactive oxygen species secretion in RAW264.7 cells.

Studies indicate that pregnant women who consume more prebiotics may lower the prevalence of IgE-mediated allergic disorders in the kids. For example, Best et al. studied how pregnant women’s intake of omega-3 long-chain PUFAs affecting the occurrence of allergic disease symptoms in their offspring. They discovered that in the first year, there was a significantly lower incidence of “sensitization to egg” and “sensitization to any food” [135]. In addition, the preventive effects of prebiotics were also evaluated in mice. Selle et al. have confirmed that GOS/inulin supplementation during pregnancy and midlactation can create a tolerogenic environment and leave a microbial imprint that shields offspring from developing wheat allergy in mice [136].

Although prebiotics have been shown in multiple studies to reduce FA, there is not enough evidence to recommend prebiotics as a standard strategy for FA prevention and treatment. Numerous high-quality RCTs and detailed mechanistic studies are needed in this area. There are hundreds of distinct HMOs, each with unique features and functions; but only a small number of HMOs have been synthesized and added to infant formula to date. Consequently, more studies are required to further examine the biological role of HMOs in the future.

4.4. Synbiotics. ISAPP revised the term synbiotic to “a mixture comprising live microorganisms and substrate(s) selectively utilized by host microorganisms that confers a health benefit on the host” [137]. In a multicenter RCT, Chatchatee et al. evaluated the safety of an amino acid-based formula (AAF) with synbiotics (AAF-S), which included the probiotic B. breve M-16V and prebiotic oligosaccharides (oligofructose and inulin) in infants with proven IgE-mediated CMA [138]. They found there was no statistically significant difference in tolerance development between the two groups. A recent meta-analysis supported this finding by demonstrating that AAF and AAF-S were equally beneficial in controlling allergy symptoms and promoting normal growth, but there were significant differences in other criteria, including infections, medications, and changes in fecal microbiota [139]. The prevalence of infections in infants fed with AAF-S was significantly reduced. When compared to AAF, children fed with AAF-S used fewer medications, and the AAF-S group’s infants had fewer hospital admissions (8.8% vs. 20.2%, p = 0.036). Fecal microbiota analysis showed that AAF-S was associated with a significantly higher abundance of Bifidobacteria and a significantly lower percentage of Eubacterium rectale and C. coccoides. In addition, 290 healthy infants between the ages of 6–19 weeks were investigated the effects of synbiotics (scGOS/lcFOS + B. breve M-16V) [140]. After 6 weeks of intervention, Bifidobacteria increased significantly and C. difficile decreased in synbiotics group. Moreover, the symbiotic groups had significantly higher levels of acetate and L-lactate as well as a significantly lower fecal pH. This RCT indicated that B. breve M-16V plus scGOS/lcFOS (9:1) could create a gut environment closer to the breastfed infants. Mechanically, B. breve M-16V treatment reconstructed the gut microbiota in terms of the increment of Actinobacteria, which was significantly decreased in infant with FA in our previous study. Furthermore, intervention with B. breve M-16V significantly boosted IL-33 expression and decreased tumorigenicity 2 (ST2) expression. Hence, they deduced that B. breve M-16V may alter the gut microbiota to reduce OVA-induced allergy symptoms by IL-33/ST2 signaling [141].

4.5. Postbiotics. In 2019, ISAPP proposed a clear definition for postbiotics as “a preparation of inanimate microorganisms and/or their components that confers a health benefit on the host” [142]. Postbiotics offer a number of desirable qualities, such as a distinctive chemical structure, safety, nontoxicity, long shelf life, enzyme resistance, and stability in the gastrointestinal tract, which provide favorable conditions for them to become novel strategies for FA treatment. Recently, Homayouni Rad et al. reviewed the existing evidence of postbiotics in FA treatment [117]. In this review, they introduced the scope, advantages, and mechanisms of postbiotics and emphasized the significant effects elicited by the SCFAs. Studies in both preclinical and clinical settings have demonstrated that SCFAs, particularly butyrate, support oral tolerance and protect against FA development. Moreover, Wegh et al. incorporated known postbiotic substances in their review, along with their postulated mechanisms, clinical data, and possible applications, such as heat-treated probiotics, endo- and exopolysaccharides (EPS), and extracellular vesicles [117]. The kefiran, the main EPS present in kefir grains, has been outstanding in recent years as a promising example of postbiotics. Existing evidence indicates that kefiran has potential beneficial effects on FA, including maintaining gut homeostasis, modulating the immune system, and balancing Th1/Th2 [143]. Thus, kefiran is among the foods that offer the best promise for treating FA without unfavorable side effects or opportunistic infections.
4.6. Fecal Microbiota Transplantation. FMT is an innovative method for reestablishing gut eubiosis. FMT is able to treat a variety of disorders, including C. difficile infection (CDI), inflammatory bowel disease, and irritable bowel syndrome, by introducing a healthy, disease-free microbiome into the patient’s gastrointestinal tract by means of stool transplants from a healthy donor to a diseased recipient [144]. FMT now has an 80%–90% cure rate for recurrent and refractory CDI. There are a few preclinical investigations as well, albeit its use in FA is restricted. Feehley et al. performed FMT on healthy and CMA infants to germ-free mice to investigate the protective impact of the gut microbiota on CMA [34]. Mice colonized with healthy donors’ feces were protected from developing anaphylactic reactions to BLG sensitization and challenge, but mice colonized with CMA donors’ feces experienced a significantly greater drop in body temperature and had higher levels of BLG-specific IgE. Recently, a mice model study revealed that FMT suppressed the allergic responses induced by OVA in atopic dermatitis mice [145]. In addition to restoring the gut microbiota, FMT also decreased IgE levels; regulated Tregs; decreased mast cells, eosinophils, and basophils; raised the amount of SCFAs; and restored the Th1/Th2 balance. FMT is a relatively simple therapeutic strategy that modifies the human gut microbiota when compared to other methods; however, to date, the research is insufficient, and its safety needs to be considered, because pathogenic factors may be introduced. Consequently, significant work is required to increase our understanding of FMT therapy for FA.

4.7. Chinese Medicine. The side effects and high cost of traditional Western treatments have led many patients to seek alternative and affordable treatments. Chinese medicine has thus gained wider and growing reputation among both the general public and medical experts in recent years, thanks to its benefits of low cost, high safety, and high biological activity. Chinese medicine has been utilized for thousands of years in Asian nations for a variety of health concerns. It is regarded as a system medicine and shares a concept with Japanese and Korean traditional medicines. In China, Korea, and Japan, it has become a part of the medical system and is used daily to prevent and treat disease [146]. Although there was no specific term for FA in traditional Chinese medicine, a practitioner (Zhang Zhongjing) created “Wu Mei Wan” to treat intestinal parasites, and we now know that these parasites can cause IgE responses; therefore, it may be used to relieve food allergy symptoms. In this context, several preclinical research and preliminary clinical investigations of Chinese herbal formulas, such as food allergy herbal formula-2 (FAHF-2), reveal an intriguing potential for FA.

FAHF-2 is the first botanical investigational novel medication for FA approved by the US Food and Drug Administration (FDA). It is produced from Wu Mei Wan. Several RCTs, preclinical studies, and reviews have been performed on it [146–149]. In a multicenter, double-blind, randomized, phase II clinical investigation, 68 FA participants between the ages of 12 to 45 received FAHF-2 or a placebo three times daily for a period of six months. FAHF-2 was shown to be both safe and well-tolerated, according to the findings. Peripheral blood mononuclear cells (PBMCs) that were stimulated with FAHF-2 demonstrated strong IL-5 suppression and increased the production of IL-10 and Tregs, suggesting that FAHF-2 has a favorable immunomodulatory effect [150]. Due to its disadvantage and high daily dosage, two refined forms of butanol purified FAHF-2 (BF2) and ethyl acetate and butanol purified FAHF-2 (EBF2) were developed. Using murine models of peanut allergy, Maskey et al. assessed the chemical stability and biological potency of FAHF-2, BF2, and EBF2. The three formulas all inhibited IgE production, with EBF2 being the most potent, suggesting that EBF2 is a clinically promising treatment for peanut allergy [151]. In addition to FAHF-2, formula-3 and a traditional Japanese herbal medicine Kakkonto were also shown to ameliorate FA [152, 153].

Although Chinese herbal medicine has been extensively utilized to treat allergy illnesses, the scientific literature lacks evidence of its effectiveness and active constituents. In addition, clinical research on FA was restricted, and sample sizes were tiny. Thus, further large-scale, long-term RCTs are required. Chinese medicine, on the other hand, has a sluggish beginning of effect and is not ideal for the treatment of large acute responses alone; thus, it is advised that Chinese medicine should be used as an adjunctive therapy for allergic illnesses.

5. Perspectives

Growing evidence from human, murine, and interventional trial observational research shows that gut microbial dysbiosis is a key component in the development of FA. Through a number of processes, the gut microbiota and its metabolites are essential in developing oral tolerance to food, such as regulating Treg differentiation, reducing basophil populations, and improving intestinal barrier function during a crucial period of early development. This imprinting mechanism might be disrupted to enhance the host’s sensitivity to FA. Therefore, the gut microbiota is becoming a new focus for FA prevention and therapy. Hence, novel therapeutic strategies that attempt to alter the gut microbiota through the use of probiotics, prebiotics, synbiotics, postbiotics, FMT, dietary modifications, and Chinese medicines may have an impact on the onset of FA and offer a viable approach for treating FA. Nevertheless, data from animal models and human research have been quite disparate, and the gut flora linked with specific food allergies may be unique. To further understand the relationships between the gut microbiota and FA, additional preclinical and clinical research is required, making the gut microbiota a potent weapon against FA in the future.

Abbreviations

2′-FL: 2′-Fucosyllactose
AAF: Amino acid-based formula
AAF-S: Amino acid-based formula (AAF) including synbiotics
APCs: Antigen-presenting cells
AHR: Aryl hydrocarbon receptor
BA: Bile acids
BF2: Butanol purified FAHF-2
BLG: β-Lactoglobulin
CDI: Clostridium difficile infection
CLA: Conjugated linoleic acids
CMA: Cow milk allergy
CNS1: Conserved noncoding sequence 1
CX3CR1+: CX3C-chemokine receptor 1
DCs: Dendritic cells
EBF2: Ethyl acetate and butanol purified FAHF-2
EHCF: Extensively hydrolyzed casein formula
EPS: Exopolysaccharides
FA: Food allergy
FAHF-2: Food allergy herbal formula-2
FDA: Food and Drug Administration
FFAR: Free fatty acid receptor
FMT: Fecal microbiota transplantation
Foxp3+ Treg cell: Forkhead box P3 regulatory T cell
FOS: Fructo-oligosaccharides
GM-CSF: Granulocyte-macrophage colony-stimulating factor
GOS: Galacto-oligosaccharides
GPCR: G protein-coupled receptor
HMOs: Human milk oligosaccharides
IDO: Indoleamine 2,3-dioxygenase
IgA: Immunoglobulin A
IgE: Immunoglobulin E
IL: Interleukin
ILC2s: Group 2 innate lymphoid cells
ILC3s: Type 3 innate lymphoid cells
IPA: Indole 3-propionic acid
ISAPP: International Scientific Association for Probiotics and Prebiotics
LGG: Lactobacillus rhamnosus GG
M cell: Microfold cell
MLN: Mesenteric lymph nodes
MUC-2: Mucin 2
MyD88: Myeloid differentiation primary response 88
OIT: Oral immunotherapy
OTUs: Operational taxonomic units
OVA: Serum ovalbumin
PAMPs: Pathogen-associated molecular patterns
PBMC: Peripheral blood mononuclear cell
PRR: Pattern recognition receptor
PUFA: Polyunsaturated fatty acids
PXR: Pregnane X receptor
RA: Retinoic acid
RALDH: Retinal dehydrogenase enzyme
RCT: Randomized controlled trial
RORγt: Retinoic acid-related orphan receptor gamma t
SCFAs: Short-chain fatty acids
ST2: Tumorigenicity 2
Tregs: Regulatory T cells
TGF-β: Transforming growth factor-β
TLR: Toll-like receptor
Th2 cell: T helper 2 cell
TSLP: Thymic stromal lymphopoietin.

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
YC, ZL, MPS, and XZ designed the contents and revised the manuscript. YC performed the literature search and wrote the manuscript. YC, XL, FC, ZL, and XZ conducted the literature search and analyzed the literature. YC, ZL, BMR, and FC prepared figures and edited the manuscript. All the authors approved the final version of the manuscript.

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