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To cite this article: Huming Shao, Fangfang Min, Meijia Huang, Zhongliang Wang, Tianliang Bai, Min Lin, Xin Li & Hongbing Chen (2022): Novel perspective on the regulation of food allergy by probiotic: The potential of its structural components, Critical Reviews in Food Science and Nutrition, DOI: [10.1080/10408398.2022.2105304](https://doi.org/10.1080/10408398.2022.2105304)

To link to this article: <https://doi.org/10.1080/10408398.2022.2105304>



Published online: 01 Aug 2022.



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REVIEW



Novel perspective on the regulation of food allergy by probiotic: The potential of its structural components

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ABSTRACT

Food allergy (FA) is a global public health issue with growing prevalence. Increasing evidence supports the strong correlation between intestinal microbiota dysbiosis and food allergies. Probiotic intervention as a microbiota-based therapy could alleviate FA effectively. In addition to improving the intestinal microbiota disturbance and affecting microbial metabolites to regulate immune system, immune responses induced by the recognition of pattern recognition receptors to probiotic components may also be one of the mechanisms of probiotics protecting against FA. In this review, it is highlighted in detail about the regulatory effects on the immune system and anti-allergic potential of probiotic components including the flagellin, pili, peptidoglycan, lipoteichoic acid, exopolysaccharides, surface (S)-layer proteins and DNA. Probiotic components could enhance the function of intestinal epithelial barrier as well as regulate the balance of cytokines and T helper (Th) 1/Th2/regulatory T cell (Treg) responses. These evidences suggest that probiotic components could be used as nutritional or therapeutic agents for maintaining immune homeostasis to prevent FA, which will contribute to providing new insights into the resolution of FA and better guidance for the development of probiotic products.

KEYWORDS

Food allergy; gut microbiome; probiotic components; immunomodulatory; anti-allergic potential

Introduction

Food allergy (FA) is defined as adverse immune response that occurs reproducibly upon exposure to given foods, which mainly refer to “The Big Eight” including milk, eggs, peanuts, soy, nuts, wheat, crustaceans and fish (Hamad and Burks 2017). Sesame is another main culprit food of triggering FA that already considered as a major allergen by Israel and Canada. There are extensive epidemiological data to suggest FA is common that up to 10% affected (Sicherer and Sampson 2018). The estimated prevalence of FA amongst children is 7.6% in United States and 8% in Western countries, while 10.8% and nearly 5% in adults respectively (Gupta et al. 2019; Sampath et al. 2021; Sicherer and Sampson 2014). In China, the prevalence of FA ranges from 3.13% to 11.9% in the northern regions and 3.5% to 21.13% in the southern regions (Tang et al. 2019). Moreover, the prevalence of FA maintains an upward trend that increasing with approximately 1.2% per decade over the past few decades (Sicherer and Sampson 2018).

FA is a global public health concern, which seriously affects the quality of life in allergic-individuals. Once exposed to food allergens, the allergic-individual could present clinical symptoms of FA such as urticaria, diarrhea,

wheezing, a life-threatening anaphylactic shock and even to death. There is increasingly widespread concern of FA that driven by the development of medical technology, the improvement of health awareness and information dissemination efficiency, especially in urban areas. How to get rid of FA is the most concerned issue for the patients. Currently, the avoidance of food allergens and emergency medication with adrenaline remain the standard of care for individuals with FA. Innovatively preventive and therapeutic approaches to surmount the challenges of FA are being developed, such as allergen-specific immunotherapy, biotherapy and microbiota-targeted therapy, and the potential effect of these therapies were demonstrated in numerous studies (Han, Krempski, and Nadeau 2020; Mayorga et al. 2021; Yu, Freeland, and Nadeau 2016).

The relationship between the gut microbiome and FA was highlighted in the previous studies and being deeply investigated. As demonstrated in human cohort studies, the individuals with FA have distinguishing gut microbiomes compared to healthy control subjects, while dysbiosis precedes the development of FA (Bunyanich and Berin 2019). The gut microbiome is a critical factor affecting FA that the composition of intestinal microbiota can imprint susceptibility or resistance to FA, and the mechanism for

maintaining immune tolerance to foods primarily involves the enhancement of intestinal barrier function and the induction of protective Tregs (Bunyavanich and Berin 2019; Wang et al. 2021).

Microbiota-based therapy holds enormous potential as a strategy for alleviating FA in view of the crucial role of microorganisms in FA. Probiotics, prebiotics, synbiotics and fecal microbiota transplantation are emerging interventions as microbiota-based therapies to regulate the gut microbiome toward beneficial outcomes in FA (Nie, Luo, and Lin 2018; Yang et al. 2021). The acceptability and safety of probiotics extend their application in the prevention and treatment of FA with significant effects (Canani et al. 2012), but the underlying mechanisms by which probiotics regulate FA are not entirely understood, especially for the specific active ingredients. According to the current evidences, it is the mainstream and verified viewpoint that probiotics could modulate the composition of intestinal microbiome and metabolites, thereby improving the intestinal barrier function and regulating immune homeostasis to prevent the occurrence of FA (Sestito et al. 2020). Interestingly, specific components of probiotic may also be the initiator to FA relief, and comprehending the potential influence of these components on the pathogenesis and process of FA will contribute to the deeply understanding of the anti-allergic effects of probiotic.

In this review, we initially summarize the pathogenesis of FA and then provide evidences for supporting the important role of gut microbiome in preventing FA, followed by a description of the beneficial impacts and main mechanisms of probiotic in regulating FA. Subsequently, we provide, for the first time, a systematic discussion that probiotic components including the flagellin, pili, peptidoglycan, lipoteichoic acid, exopolysaccharides, surface (S)-layer proteins and DNA may serve as immunomodulatory factors to modify the development of FA. It will help to the design of probiotic components-based intervention and therapeutic strategies for modulating the immune disorder of allergic individuals to prevent FA.

The pathogenesis of FA

The common mechanism of FA is the breakdown of immunologic tolerance to the ingestion of innocuous food, which induces immunoglobulin E (IgE)-mediated, non-IgE-mediated and mixed-mediated FA reactions. IgE-mediated hypersensitivity responses occur rapidly with clinical symptoms typically developing within minutes to a few hours after ingestion of the offending food, whereas non-IgE and mixed-mediated reactions are usually chronic and may be more intricate (Sicherer and Sampson 2018). IgE-mediated type, associated with severe or fatal anaphylaxis, is the most fully characterized class of FA and its immune mechanisms will be exclusively focused next.

Food allergens can be transported through the epithelial barrier via several mechanisms including paracellular diffusion, transcytosis through enterocytes, goblet cell-associated antigen passages, endocytosis by microfold cells and directly

sampling from the lumen by intestinal CX3CR1⁺ macrophages and CD103⁺ dendritic cells (DCs) extending dendrites between enterocytes (Liu, Yin, et al. 2020; Tordesillas and Berin 2018). Another transport mechanism was raised recently in a murine model that food allergens could be channeled across the epithelium by intestine secretory epithelial cell antigen passages mediated by the interleukin (IL)-13/CD38/cyclic adenosine diphosphate ribose (cADPR) pathway, regulating the onset of food induced anaphylaxis (Noah et al. 2019). These molecular processes were conserved in human intestine (Noah et al. 2019). The epithelial cells stimulated by allergens upregulate the secretion of inflammatory mediators such as IL-33, IL-25 and thymic stromal lymphopoietin (TSLP) and act upon DCs and innate lymphoid cells, to further promote Th2 skewing (Sampson et al. 2018). These mediators activate group 2 innate lymphoid cells (ILC2s) to produce large amounts of Th2 cytokines (such as IL-4 and IL-13) and upregulate OX40 ligand (OX40L) on DCs. The interaction between OX40L on DCs and OX40 on naïve T cells shifts the differentiation from naïve T cells into Th2 cells (Anvari et al. 2019; Sampson et al. 2018). Th2 lymphocytes and associated proinflammatory cytokines promote B-cell proliferation, drive B cells class switching to produce IgE and expansion of allergic effector cells. The allergens specific IgE (sIgE) immediately crosslink with the high-affinity IgE receptor (FcεRI) on the surface of mast cells and basophils, which triggers the degranulation resulting in the release of mediators such as histamine, prostaglandins, leukotrienes and cytokines. This induces a series of inflammatory responses and ultimately leads to the allergic manifestations (Figure 1).

The involvement of microbiome in FA

Risk factors related to environment (e.g., excessive cleanliness) and Western lifestyle such as high fat and low fiber diets are considered to be the culprits for the rapid increase in the prevalence of FA. These factors are associated with the changes of gut microbiota, and therefore may exert their effects through the microbial influence on the mucosal immune system (Tordesillas, Berin, and Sampson 2017).

Microbial balance is essential for the development and maturation of immune system. Growing evidence indicated that the gut microbiomes of patients with FA manifested early onset dysbiosis (Abdel-Gadir et al. 2019; Bunyavanich and Berin 2019). Compared with healthy individuals, increased α -diversity and distinct taxa characterized the early-life gut microbiome of children with egg allergy (Fazlollahi et al. 2018). Altered microbiota was also observed in children with cow's milk allergy (CMA), and Firmicutes were found to be enriched in the early life gut microbiome of subjects with milk allergy resolution (Bunyavanich et al. 2016). In addition, evidence from the healthy and allergic twins suggested that Clostridia class were enriched in healthy twins, and the species (*Phascolarctobacterium faecium* and *Ruminococcus bromii*) related to fecal metabolome of healthy were also identified (Bao et al. 2021). Although previous studies have characterized the composition of the microbes

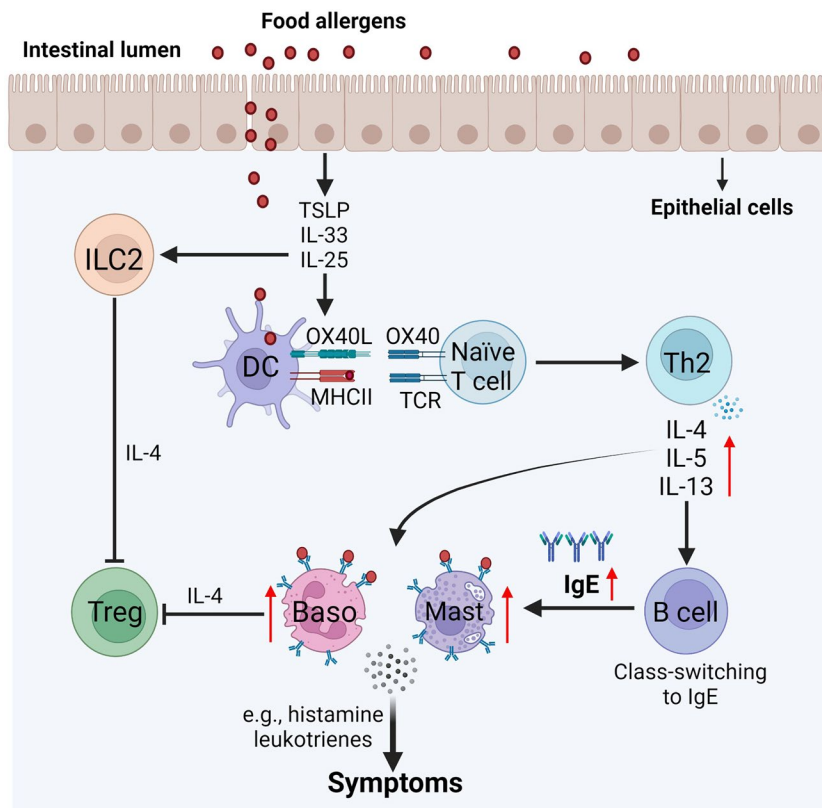


Figure 1. Mechanism of IgE-mediated FA. The epithelial cells stimulated by allergens upregulate the secretion of IL-33, IL-25 and TSLP. These mediators upregulate OX40 ligand (OX40L) on DCs, priming naïve T cells toward a Th2 cell responses. ILC2s are also activated to produce large amounts of IL-4 and other Th2 cytokines, which suppress generation of Tregs and promote Th2 cell responses. Th2 lymphocytes and associated cytokines promote B-cell proliferation, drive B cells class switching to produce IgE and expansion of mast cells and basophils. The allergens specific IgE immediately crosslink with the high-affinity IgE receptor (FcεRI) on the surface of effector cells, which triggers the degranulation resulting in the release of mediators such as histamine and leukotrienes, and ultimately leads to a series of clinical symptoms.

in patients with FA, there is a lack of information on the functional consequences of differences in microbial composition. Recently, functional profiling of intestinal microbiome revealed that *Ruminococcus gnavus*, significantly enriched in the gut of allergic children, has pro-inflammation potential and lower fiber degrading ability (De Filippis et al. 2021). Notably, despite rapid progress in the field, the understanding of the gut microbiome and FA based on human cohort studies is still in its infancy, and the exact relationship between them remains not fully clear.

In addition to direct observational evidences from population-based studies, the establishment of Germ-free (GF) mice further clarified the critical role of “normal” commensal bacteria in preventing FA. Despite the inconsistent results, most studies have shown that GF mice were highly susceptible to food-induced anaphylaxis exhibited higher IgE responses (Abdel-Gadir et al. 2019; Feehley et al. 2019; Schwarzer et al. 2019; Stefka et al. 2014). The GF-mice colonized with bacteria from healthy, but not CMA, were protected against allergic responses to cow’s milk protein (Feehley et al. 2019). Importantly, the interaction of commensal bacteria with host immune system favors to promote immune tolerance via the regulation of the Tregs development (Faith et al. 2014; Stephen-Victor, Crestani, and Chatila 2020). The colonization of ovalbumin (OVA)/

SEB-sensitized GF Il4ra^{F709} mice with Clostridiales consortium that deficient by dysbiosis increased the frequency of gut ROR-γt⁺ Tregs and inhibited the FA-associated Tregs reprogramming to Th2-cell like phenotype, while abrogated the protection by aforementioned bacteria in FA when deletion of myeloid differentiation primary response 88 (Myd88) or Rorc (encoding ROR-γt) in Tregs (Abdel-Gadir et al. 2019). Besides, the commensal bacteria play an important role in maintaining the function of intestinal mucosal barrier. Colonization of *Clostridia*-containing microbiota induced the production of IL-22 by group 3 innate lymphoid cells (ILC3s) in the colonic lamina propria and stimulated the goblet cell for mucus secretion and paneth cell for antimicrobial peptides (AMPs) production to fortify intestinal barrier function and reduce the permeability of the intestine to dietary proteins (Stefka et al. 2014). The reinforcement of intestinal barrier function reduces the possibility of allergens into the systemic circulation, contributing to the prevention of allergic sensitization. More detailed evidences on the mechanisms by which the gut microbiome regulates FA are well described in a review published latterly (Wang et al. 2021). Given the critical effects of microbes on immune system, it is reasonable that microorganisms are fertile targets for the prevention and treatment of FA.

The role of probiotic in preventing FA

Probiotics have been defined as “live microorganisms that confer a health benefit on the host when administered in adequate amounts”. Numerous studies have shown immunomodulatory effects of some Lactobacillaceae and Bifidobacteriaceae strains such as *Lactobacillus rhamnosus* GG (LGG), *Lactobacillus plantarum* and *Bifidobacterium breve*. Current studies have presented strong evidences supporting that probiotics supplement may be an effective approach to prevent FA by providing direct or indirect signals (such as the modulation of the gut microbiota) to facilitate immune tolerance (Renz and Skevaki 2021).

Dietary management with extensively hydrolyzed casein formula (EHCF) containing LGG accelerated acquisition of tolerance in infants with CMA when compared to subjects receiving EHCF alone (Canani et al. 2013). Subsequently, it was further demonstrated that LGG enhanced tolerance acquisition in infants with CMA, partly, by affecting the strain-level bacterial community structure (mainly as increased abundance of butyrate-producing bacteria) (Canani et al. 2016). Butyrate acts as a histone deacetylase inhibitor that increases histone H3 acetylation of Foxp3 gene locus, therefore, promoting the development of Tregs (Liu et al. 2018). Its regulatory effect on Tregs is mediated by G protein-coupled receptor 43, which has been identified as an important short-chain fatty acid (SCFA) receptor (Furusawa et al. 2013; Tan et al. 2016). Moreover, supplementation of probiotic could influence gut microbiome function. A cohort trial of 25 infants at high-risk for asthma randomized to daily oral supplementation of LGG (HRLGG) or placebo for 6 months indicated that microbial metabolism within the HRLGG infants was more similar to that of healthy. Specifically, HRLGG infants were characterized by the enrichment of a variety of lipid androgenic steroids known to provide protection against various inflammatory conditions (Durack et al. 2018). Meanwhile, coadministration of probiotic *Lactobacillus rhamnosus* CGMCC 1.3724 and peanut oral immunotherapy (PPOIT) in children with peanut allergy for 18 months could reduce sIgE levels, increase sIgG4 levels and induce higher rate of desensitization (Tang et al. 2015). Notably, PPOIT has been demonstrated to provide long-lasting clinical benefits and persistent suppression of the allergic immune responses to peanut, suggesting that probiotics can be used as microbial adjuvants for oral immunotherapy of FA (Hsiao et al. 2022; Hsiao et al. 2017).

In view of the limitations of clinical trials, the positive outcomes of probiotics in FA are more obtained from pre-clinical studies. Probiotics could alleviate FA through various underlying mechanisms that may varied from the difference of probiotic strains and experimental models used in studies. In the OVA-induced FA murine model, oral supplement of *Bifidobacterium breve* M-16V may alter the gut microbiota composition to ameliorate OVA-induced allergic symptoms through the IL-33/suppression of tumorigenicity 2 (ST2) signal pathway (Li et al. 2020). Similarly, oral administration with *Lactobacillus plantarum* CCFM1189, *Lactobacillus*

reuteri CCFM1190 and *Bifidobacterium longum* CCFM1029 could decrease OVA-specific IgE level and ameliorate the pathological symptoms of OVA-induced FA mice (Lu et al. 2022). These probiotics could alter the composition of gut microbiota. For example, CCFM1189 intervention increased the abundance of *Akkermansia*, while CCFM1029 enriched *Bifidobacterium* and SCFA-production bacteria (e.g., *Dubosiella*). Furthermore, CCFM1189 and CCFM1190 improved the level of indoleacrylic acid, which could bind to the aryl hydrocarbon receptor and promote the transcription of IL-22. In addition to OVA-induced allergy models, *Lactobacillus casei* Zhang could alleviate shrimp tropomyosin allergy through directly promoting tolerogenic CD103⁺ DC and Tregs development, maintaining Th1/Th2 homeostasis and directing B cells to produce tolerogenic IgA (Fu et al. 2020). Similar results were obtained in a β -lactoglobulin (BLG)-induced allergic mouse model, in which *Lactobacillus plantarum* ZDY2013 and *Lactobacillus plantarum* WLPL04 could inhibit the Th2-biased allergic response by regulating Th1/Th2 immune balance and enhancing intestinal barrier function (Fu et al. 2019). In all, probiotics supplementation can reshape the intestine microbial environment and contribute to the balance of gut microbiota, alternation of microbial metabolites, maintenance of intestine barrier integrity, and regulation of the immune responses (Figure 2). These immunomodulatory effects of probiotics endow them with the ability to promote immune tolerance in response to food allergens and thus protecting against the development of FA.

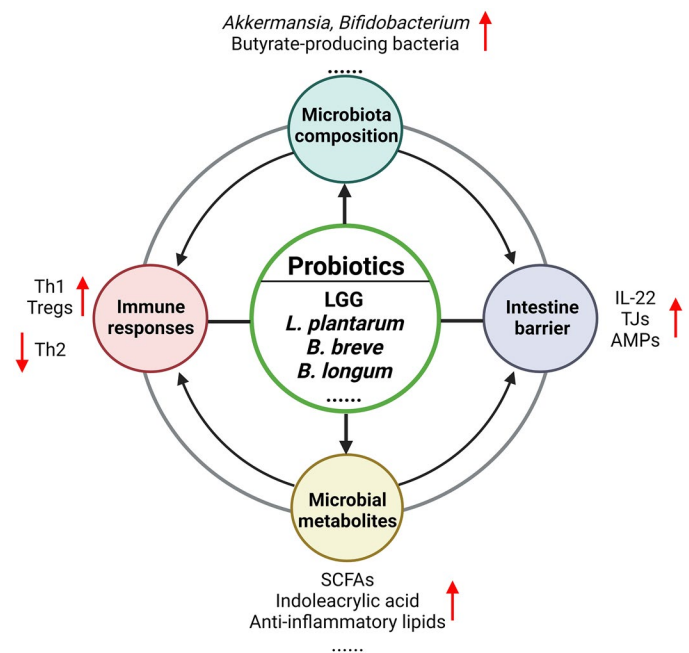


Figure 2. The main mechanism of probiotics in the prevention of FA. Supplementing with probiotics (mainly *Lactobacilli* spp. and *Bifidobacteria* spp.) can reshape the intestine microbial environment in food allergy patients and contribute to improving gut microbiota composition, altering microbial metabolites, maintaining intestine barrier integrity and regulating immune responses, thereby exerting anti-allergic effects. LGG, *Lactobacillus rhamnosus* GG; SCFAs, short-chain fatty acids; TJs, tight junctions; AMPs, antimicrobial peptides.

Effect of probiotic components on immune system and potential to modulate FA

Probiotic is one of the most effective microbiota-management tools for regulating intestinal homeostasis. Reverse of the imbalance intestinal microbiome, protection of the intestinal barrier function and regulation of Th1/Th2/Treg balance are considered to be the main anti-allergic mechanisms of probiotic. Interestingly, there are evidences for the positive effects of inactivated bacteria in the treatment of allergic disease, except to the beneficial effects of live bacteria.

Improvement in allergic symptoms was reported in NC/Nga mice (commonly used to establish mouse model of atopic dermatitis) given heat-treated *Lactobacillus crispatus* KT strains, showing a significant decrease in serum IgE levels and an increase ratio of IFN- γ^+ CD4 $^+$ /IL-4 $^+$ CD4 $^+$ in the spleen (Tobita, Yanaka, and Otani 2009). In addition, supplementation with heat-killed LGG both significantly reduced the Scoring Atopic Dermatitis scores in 35 infants with atopic eczema and CMA (Kirjavainen, Salminen, and Isolauri 2003). Notably, postbiotics, defined as preparation of inanimate microorganisms and/or their components, have been proven to benefit host health (Rad et al. 2021; Sabahi et al. 2022; Salminen et al. 2021). As one of the postbiotic

ingredients, the structural components of probiotic (such as flagellin, peptidoglycan and lipoteichoic acid) have attracted considerable attention on anti-allergic effects. In this section, the regulatory potential with regard to FA of probiotic components will be discussed based on the interaction of these components with immune system (Figure 3).

Flagellin

Flagellin is the essential component of flagellum (a surface structure for propelling bacterium into appropriate niches). Traditionally, flagellin was considered as a virulence factor that contributes to the adhesion and invasion of host cells, but now it is emerging as a potent immune activator for disease treatment.

Flagellin is the bacterial stimulus to trigger toll-like receptor (TLR) 5, which is widely expressed at the surface of epithelial cells, macrophages, DCs and lymphocytes (Vijayan et al. 2018). Flagellin recognition by TLR5 triggers the signaling of MyD88 and downstream nuclear factor kappa B (NF- κ B), mitogen-activated protein kinase (MAPK), and interferon-regulatory factor (IRF) pathways (Figure 4), thereby activating innate and adaptive immune responses.

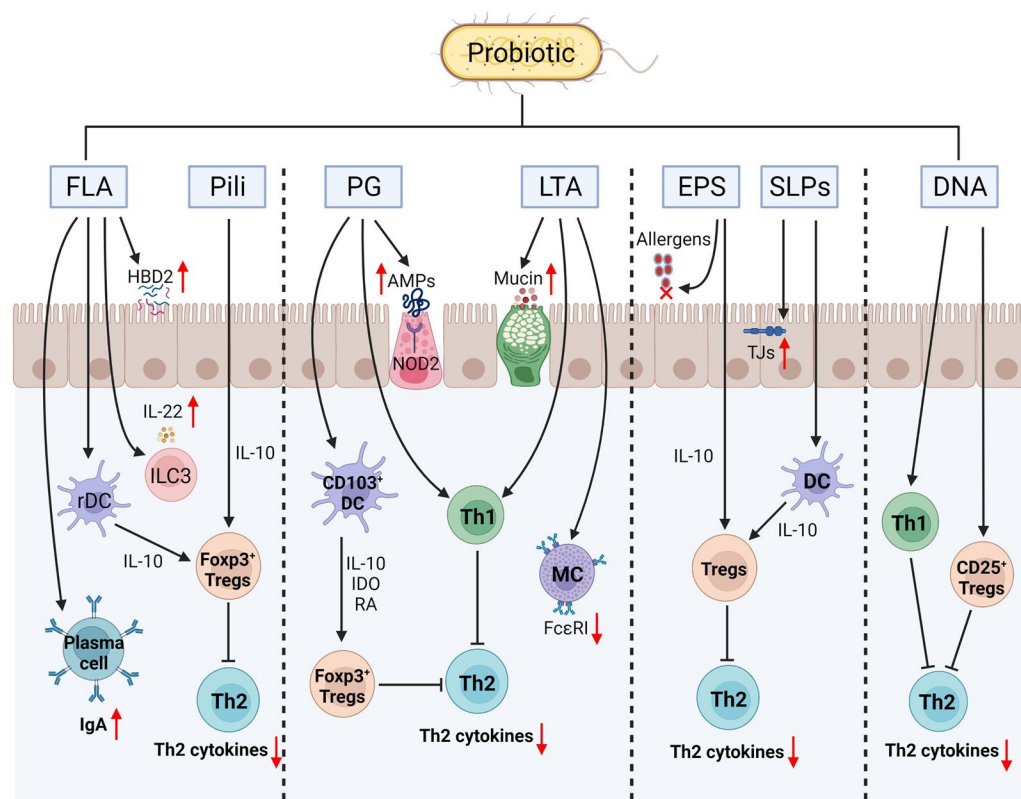


Figure 3. The underlying mechanisms of FA regulation by probiotic components. Flagellin can promote the secretion of HBD2, IL-22 and IgA to enhance intestinal barrier function. Flagellin regulates the generation of rDCs and enhance Tregs in an IL-10-dependent manner. Pili also promotes differentiation of Tregs, then, inhibiting Th2 responses. Activation of NOD2 by PG could enhance epithelial barrier function via promoting the secretion of antimicrobial peptides in paneth cells. PG promotes the differentiation of CD103 $^+$ DCs and favors the conversion of CD4 $^+$ Foxp3 $^+$ Tregs by producing IL-10, IDO and RA. On the other hand, PG and LTA could enhance Th1 response, therefore correcting Th2-biased allergic reactions. LTA protected the intestinal barrier by enhancing the expression of Muc2, and suppressed the IgE-induced degranulation of MCs by reducing expression of Fc ϵ RI receptors. EPS could reduce the expression of Th2 cytokines in IL-10-dependent manner and relieve allergy by isolating the allergens. Promotion of TJs and IL-10 mediated by SLP contribute to preventing FA. DNA can reverse the bias of Th2 by inducing Th1 responses and promoting the differentiation of Tregs. FLA, flagellin; PG, peptidoglycan; LTA, lipoteichoic acid; EPS, exopolysaccharides; SLPs, surface (S)-layer proteins; HBD2, human beta-defensin 2; rDC, regulatory dendritic cell; IDO, indoleamine 2,3-dioxygenase; RA, retinoic acid; MC, mast cell.

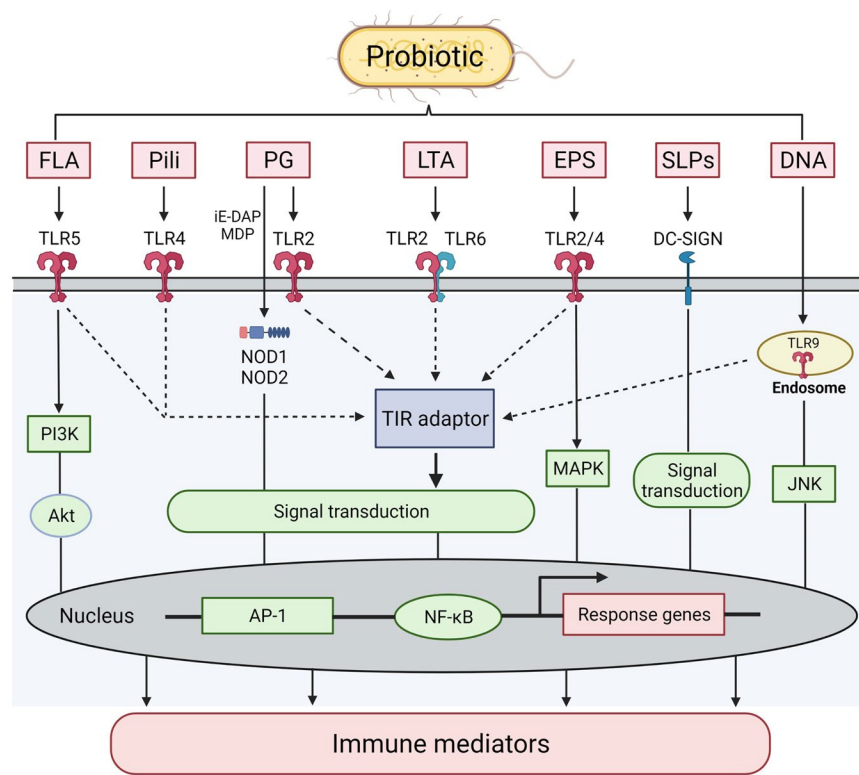


Figure 4. Interactions between probiotic components and pattern recognition receptors and associated signaling events. Probiotic components can be recognized by pattern recognition receptors such as TLRs, NODs and DC-SIGN, thus causing downstream signal transduction to activate AP-1 and NF-κB signaling pathways, eventually inducing the production of immune mediators. TLRs, toll-like receptors; DC-SIGN, dendritic cell-specific intercellular adhesion molecule 3-grabbing non-integrin; NOD1, nucleotide-binding oligomerization domain 1; NOD2, nucleotide-binding oligomerization domain 2; MDP, muramyl dipeptide; iE-DAP, γ-D-glutamyl-meso-diaminopimelic acid; TIR, Toll/interleukin-1 (IL-1) receptor; PI3K, phosphoinositol 3-kinase; MAPK, mitogen-activated protein kinase; JNK, c-Jun N-terminal kinase; AP-1, activating protein-1; NF-κB, nuclear factor kappa B.

Flagellin can also be recognized by NAIP5 and NAIP6 (NLR family, apoptosis inhibitory proteins) when delivered to the cytoplasm of host cells (Kofoed and Vance 2011). The flagellin-bound NAIP5/6 complexes interact with nucleotide-binding oligomerization domain-containing proteins (NOD)-like receptor NLRC4, which leads to the activation of IL-1β and exerts pro-inflammatory effect. Although flagellin is generally considered to show strong immune activating effects, some studies have revealed the opposite results. Treatment with *Salmonella* flagellin CBLB502 significantly reduced the expression of NF-κB and TLRs in the TNBS-induced ulcerative colitis mice (Xu et al. 2016). Furthermore, the rapid activation of phosphoinositide 3-kinase (PI3K) by the binding of flagellin to epithelial TLR5 can relieve inflammation via inhibiting the MAPK signaling pathway (Bao et al. 2015; Song et al. 2017).

It is noteworthy that bacterial flagellin could enhance the defensive ability of the epithelial barrier (Liu, Yu, et al. 2020). Schlee et al. clearly showed that flagellin of probiotic *Escherichia coli* Nissle 1917 (EcN) induced the expression of the human beta-defensin 2 (HBD2) synthesized by intestinal epithelial cells (IECs) to counteract bacterial invasion (Schlee et al. 2007). Additionally, administration of flagellin exacerbated the production of IL-22, a crucial cytokine in antimicrobial defense in intestinal mucosa, indicating that flagellin have the potential to protect intestinal barrier (Van Maele et al. 2014). Enhanced intestinal barrier function

could decrease food allergens access and then may modify the occurrence of FA.

The immunomodulatory capacity of flagellin in the regulation of Tregs and IgA responses demonstrates that flagellin has the potential to alleviate allergic diseases. Several studies have reported the positive effect of flagellin on allergic diseases. For example, intranasal co-administration of flagellin with OVA could significantly inhibit OVA-induced airway hyperresponsiveness, eosinophilic airway inflammation and the Th2 cytokines production in OVA-sensitized mice (Lee et al. 2008). Similarly, intranasal treatment with a mixture of flagellin B (FlaB) and OVA was also shown to ameliorate OVA-induced asthma by suppressing Th1/Th2/Th17 responses in a TLR5-dependent manner via the generation of regulatory DCs (rDCs) and Tregs, and a similar effect of flagellin was observed in house-dust mite (HDM)-induced asthmatic mice (Shim et al. 2016). In addition, the effect of flagellin was reproduced in peripheral blood mononuclear cells (PBMCs) from patients with HDM-sensitive asthma that flagellin treatment could generate rDCs in PBMCs and enhance Tregs through an IL-10-dependent mechanism (Shim et al. 2016). Intriguingly, the coexistence way of flagellin and allergen is associated with the immunoregulation capacity, it was demonstrated that HDM allergen Derp2-FlaB fusion protein was more efficacious in inhibiting Derp2-specific IgE production and Th2 response than the mixture of

Derp2 plus FlaB (Tan et al. 2019). Numerous studies have also confirmed the inhibitory effects of flagellin and allergen fusion on experimental allergic reactions (Kim et al. 2016; Kitzmuller et al. 2018; Schulke et al. 2011). Furthermore, flagellin is an excellent mucosal adjuvant for augmenting protective IgA production, which is thought to be related to immune exclusion and mucosal homeostasis (Dzidic et al. 2017). Recently, the critical role of flagellin in alleviating experimental FA has been revealed that flagellin can form complexes with FcγRI on eosinophil to maintain eosinophil at static condition in the intestine (Luo et al. 2021; Lv et al. 2022). Overall, these findings about the effects of flagellin on protection of intestinal barrier, inhibition of inflammation and induction of Tregs collectively provide compelling evidences for flagellin relieving allergic diseases, although it may be affected by bacterial species and dosage. The immunomodulatory functions of flagellin and its impact factors need to be further explored that may provide a potential therapeutic candidate for allergic diseases including FA.

Pili or fimbriae

Pili (or fimbriae) have been regarded as a key colonization factor for adhesion and niche adaptation in commensals. It is described as long and non-flagellar proteinaceous appendages on the cell surface of specific bacteria (mainly Gram-negative bacteria) to mediate the initial contact of bacteria with host cells. To date, various types of pili have been identified, including chaperone-usher pili, type IV pili, conjugative type IV secretion pili, curli pili, type V pili and sortase-dependent pili according to the criteria such as secretion system, construction and function (Hospenthal, Costa, and Waksman 2017; Sharma, von Ossowski, and Krishnan 2021).

The strong adhesion of probiotics mediated by pili largely contributes to their subsequently beneficial effects. Tight adherence (Tad) pili from *Bifidobacterium breve* UC2003 is not only an essential factor for bacterial colonization, but also promotes the proliferation of epithelial cells and thereby may facilitates early gut maturation, which is mediated by the pilin subunit TadE (Motherway et al. 2019). In recent years, studies have suggested that pili are closely related to the stimulation or regulation of host immune system. For instance, the sortase-dependent pili from *Bifidobacterium bifidum* PRL2010 induced a higher tumor necrosis factor-α (TNF-α) response during the colonization in mice (Turrone et al. 2013). Moreover, SpaCBA pili of LGG were demonstrated as a key factor in inhibiting proinflammatory marker IL-8 mRNA expression in IECs induced by the interaction of lipoteichoic acid (LTA) with TLR2 (Lebeer, Claes, Tytgat, et al. 2012). Recently, a study has shown the potential of pili in alleviating allergic diseases. Enterobacterial fimbriae H (FimH) as an adjuvant significantly enhanced the effect of allergen specific immunotherapy on improvement of asthma phenotype and reduction of serum IgE levels in HDM-induced asthmatic mice, which involved the mechanism that FimH triggered the expression of IL-10 and promoted the

differentiation of Tregs perhaps via activating TLR4 signaling pathway (Yang et al. 2020). Hence, some structurally distinct pili types play diverse functional not only including adhesion but also immunomodulatory activity that can be considered as a potentially effective strategy for promoting health benefits.

Peptidoglycan

Peptidoglycan (PG) is a compound carbohydrate molecule found in the cell wall of both Gram-positive and Gram-negative bacteria and consists of peptides and glycans. The main structural features of PG are linear glycan strands cross-linked by short peptides. Although the main structure of the bacterial PG is similar with both backbone and cross-linking modifications (Wolf and Underhill 2018), the degree of crosslinking and sugar chain length vary greatly among different bacteria, which may serve as the basis responsible for the functional difference of PG.

The innate immune system senses intact PG and PG fragments based on numerous pattern recognition receptors that can be divided into peptidoglycan recognition proteins (PGLYRPs), TLRs (mainly TLR2) and NOD-like receptors (NLRs) (Wolf and Underhill 2018). The binding of PGLYRPs to PG activated the oxidative stress response and enhanced the phagocytosis ability of phagocytes to bacteria by recognizing the muramyl pentapeptide or tetrapeptide (De Marzi et al. 2015; Kashyap et al. 2017; Kashyap et al. 2011). It was reported that TLR2-deficient macrophages were hyporesponsive to several Gram-positive bacterial cell walls as well as *Staphylococcus aureus* PG, indicating a major role of TLR2 in PG recognition (Takeuchi et al. 1999). However, it remains controversial whether PG can activate TLR2. Multiple confirmatory studies have shown that PG cannot activate TLR2, which attribute to the diversity of PG structure and the differences in purification methods (Wolf and Underhill 2018), even though there are still studies reporting that PG induces TLR2 activation and triggers inflammation (Wang et al. 2019). Therefore, a viewpoint is tended to be accepted that PG monomer only synergistically activate cells with other defined TLR2 ligands.

Recognition of PG by NLRs plays a vital role in the process of immune signal transduction. Short peptide chains of 3–5 amino acids in the PG are diverse among bacteria and could be recognized by NLRs differentially. Generally, γ-D-glutamyl-meso-diaminopimelic acid and muramyl dipeptide structures from both Gram-positive and Gram-negative bacteria are recognized by NOD1 and NOD2 respectively (Figure 4). Notably, the sensing of bacterial PG by NOD1 is implicated with the enhancement of anti-infection. For instance, the increased susceptibility of Nod1^{-/-} mice to early pneumococcal sepsis demonstrated a role for NOD1 in priming innate immune defenses promoting a rapid response to infection (Clarke et al. 2010). Meanwhile, the activation of NOD2 could enhance epithelial barrier function and protection from damage via facilitating the secretion of AMPs by paneth cells expressed high levels of NOD2 (Wolf and Underhill 2018). In addition, NOD2-mediated sensing to PG has been demonstrated to regulate the establishment of T

cell subsets. The stimulation of *Lactobacillus salivarius* Ls33 PG on NOD2 could promote the differentiation of CD103⁺ DCs and migrate to the draining mesenteric lymph nodes, as well as favor the conversion of naïve CD4⁺ T cells into CD4⁺ Foxp3⁺ Tregs by producing IL-10, indoleamine 2,3-dioxygenase and retinoic acid (Fernandez, Pot, and Grangette 2011; Macho Fernandez et al. 2011). On the other hand, the inflammatory development of childhood asthma and atopic diseases may be associated with the loss of sensing to bacterial PG fragments by NLRs (Maeda, Caldez, and Akira 2019), indicating that recognition of PG would contribute to inhibiting the development of allergic disease. Most prominently, intact PG from *Lactobacillus acidophilus* was shown to be effective in alleviating FA in a murine model of BLG allergy, manifested by the decrease of Th2 cytokines mRNA expression and significant increase of Th1 cytokines and transforming growth factor- β (TGF- β) mRNA expression, emphasizing the ability of probiotic PG to redress Th2-biased allergic response (Li et al. 2014; Li et al. 2013). Taken together, these studies supported the concept that bacterial PG-induced immune activation helps the immune system deviate from Th2 responses and plays an important role in probiotic to alleviate FA, implying that PG could constitute a viable strategy to prevent FA.

Lipoteichoic acid

Teichoic acids are classified into wall teichoic acid (WTA) and LTA according to the attached distribution on bacteria. Here, we will focus on the immunomodulatory properties of LTA, as WTA seems to be less immune stimulation than that of LTA due to the lack of lipid components (Lebeer, Claes, and Vanderleyden 2012). LTA is an essential component attached to the cell membrane in Gram-positive bacteria, and its structure is generally divided into modified structures of D-alanylation branch, glycosyl and phosphorylcholine residues. Of note, although LTA molecules share similarly structural framework, there are differences among diverse bacteria (especially between pathogenic bacteria and probiotics), that may lead to contrasting immune responses. Previous studies have reported that the content of D-alanylation and glycosyl, as well as the number of acyl chains and the degree of saturation in lipid chain play a critical role in the immune stimulation and regulation effects of LTA (Mizuno et al. 2020).

LTA is generally considered as one of the major pathogen-associated molecular patterns of Gram-positive bacteria. It can be recognized by heterodimers of TLR2/TLR6 and subsequently regulates the differentiation of immune cells and promotes the balance of pro- and anti-inflammatory cytokines, affecting the development of inflammatory. Early studies indicated that LTA mainly exerted pro-inflammatory effects, comparable to lipopolysaccharide (LPS), which could enhance the secretion of pro-inflammatory cytokines and promote the occurrence of inflammation (Lebeer, Claes, and Vanderleyden 2012). The enhanced efficacy of probiotic LTA mutant strains (complete removal of LTA, removal of the D-alanyl substitutions or shift from D-alanyl to glucosyl

substitutions) on inflammatory bowel disease (IBD) and other inflammatory diseases provided stronger evidence for LTA as a pro-inflammatory component (Claes et al. 2010; Mohamadzadeh et al. 2011). However, it should be noticed that not all LTAs behave as pro-inflammatory molecules. LTA from *Lactobacillus plantarum* decreased IL-8 production by inhibiting the activation of TLR2, p38 kinase, c-Jun N-terminal kinase (JNK) and NF- κ B transcription factor that induced by Pam2CSK4 in human IECs (Noh et al. 2015). Similar results were obtained in a TNF- α -induced inflammation model that treatment with *Lactobacillus plantarum* LTA (Kim et al. 2012). Separately, *Clostridium butyricum* LTA inhibited the activation of NF- κ B and extracellular regulated protein kinases (ERK) signaling and the release of IL-8 and TNF- α in HT-29 cells (Wang et al. 2016). Likewise, *Lactobacillus paracasei* LTA was demonstrated to reduce inflammation and protect the intestinal barrier in vivo by inhibiting NF- κ B pathway, activating TLR2-p38-MAPK signaling to enhance mucin expression (Wang et al. 2020). On the other hand, LTA contributes to the balance of Th1 and Th2 immune responses, which plays a key role in protecting against the development of FA. Horiuchi et al. found that LTA-related molecule, OK-432 (a streptococcal preparation) can regulate the shift from Th2 to Th1 predominance and remarkably reduce atopic dermatitis (AD)-like lesions in NC/Nga mice (Horiuchi et al. 2004; Horiuchi et al. 2006). On this basis, the immunoregulatory effects of LTA on allergic diseases have aroused more attention.

Initially, LTA from *Staphylococcus aureus* was demonstrated to upregulate the expression of IL-4/IL-5 mRNA and IgE levels in HDM-sensitized mice models (Matsui and Nishikawa 2002, 2003). However, staphylococcal LTA, heat-killed *Staphylococcus aureus* and lipoprotein Pam3CSK4 as TLR2 ligands were shown to inhibit Th2 cytokine (e.g., IL-5 and IL-13) responses of blood monocytes to HDM in patients with HDM allergy, which seems to be mediated by the effect of TLR2 ligand on antigen-presenting cells (Taylor, Richmond, and Upham 2006). Moreover, Yoshioka et al. found that *Staphylococcus aureus* LTA reduced the Fc ϵ RI expression and IgE-induced degranulation of human mast cells through TLR2 pathway (Yoshioka et al. 2007). Recently, several studies have reported the involvement of *Lactobacillus plantarum* LTA in ameliorating AD. Combination treatment with LTAs from *Lactobacillus plantarum* and *Staphylococcus aureus* alleviated AD symptoms by decreasing the levels of IgE and C-C motif chemokine ligand (CCL) 2 and driving the shift of Th2 response to Th1 response in an irritant contact dermatitis-induced murine model (Kim et al. 2019). Nevertheless, further research highlighted the major role of *Lactobacillus plantarum* LTA, rather than *Staphylococcus aureus* LTA in inhibiting the production of IgE and CCL2 (Kim et al. 2020). Apparently, the potential of LTA in alleviating FA could be perceived from the immunomodulatory effects of LTA in allergic diseases. Insight into the functional discrepancies of LTA from different bacteria in the modulation of immune responses and to investigate the probiotic LTAs that can effectively alleviate FA and other allergic diseases should be attractive and significative exploration.

Exopolysaccharides

Various bacterial envelope is surrounded by one or more glycan layers known as capsular polysaccharides or exopolysaccharides (EPS), which has been involved in immunoregulatory activity and protective effects of commensal bacteria. According to the types of monosaccharides and biosynthesis mechanism mediated by glycosidic linkages, EPS can be classified as homopolysaccharides and heteropolysaccharides when composed by the repetition of monosaccharide or by two and more types of monosaccharide subunits. Structural diversity of EPS enables it to be recognized by different innate immune receptors, such as TLR2 and TLR4 (Yang et al. 2022).

Numerous studies have highlighted the crucial role of EPS in health promotion involving intestinal barrier protection, regulation of intestinal microbiota composition, and suppression of inflammatory responses (Pourjafar et al. 2022; Rajoka et al. 2020). For example, EPS from *Lactobacillus plantarum* YW11 was revealed in ameliorating colonic tissue damage in mice with dextran sodium sulfate (DSS)-induced colitis effectively administered at the dosage of 10 mg/kg, and the recovery of intestinal microbial diversity as well as increase of metabolite butyrate content were observed in mice fed with EPS at 25 mg/kg (Zhang et al. 2020). Besides, EPS could reduce the secretion of pro-inflammatory cytokines (such as IL-6, TNF- α , IFN- γ) and increase the secretion of IL-10 that relieving enteritis (Zhang et al. 2020). Similarly, EPS from *Lactobacillus plantarum* NCU116 could promote intestinal homeostasis and alleviate IBD-related symptoms by regulating the proliferation and differentiation of intestinal stem cells, and increasing the abundance of microorganisms (e.g., Bifidobacteriaceae and Lactobacillaceae) that related to intestinal regeneration (Zhou et al. 2021). The anti-inflammatory capacity of EPS was also demonstrated in macrophages that the intermediate polysaccharide chains of EPS from *Lactobacillus rhamnosus* decreased the levels of TNF- α , IL-6 and increased IL-10 production (Bleau et al. 2010).

In addition, several achievements were made on EPS regarding impacts on the activation and differentiation of T cells, especially on Treg and Th17 cells. The presence of surface EPS from *Bifidobacterium longum* 35624 is essential for dampening the pro-inflammatory responses and local Th17 response revealed in colitis mice model and OVA respiratory allergy model, whereas the loss of EPS accompanied by enhanced recruitment of IL-17⁺ CD4⁺ T lymphocytes (Schiavi et al. 2016). Simultaneously, EPS from *Bifidobacterium adolescentis* strain IF1-03 significantly increased the proportion of Treg/Th17 cells for restraining an excessive effector T cell response in intestinal mucosa, and activated macrophage dependent on the TLR2-ERK/p38 MAPK-signaling cascade (Yu et al. 2019). In contrast, *Lactobacillus casei* EPS promoted the differentiation of CD4⁺ T cells into Th17 cells in healthy mice and improved intestinal mucosa immunity (Ren et al. 2020). The inconsistent results may indicate the immunomodulatory specificity of EPS from diverse strains for host in different health states. Intriguingly, the specificity may be owed to the charge or

size of EPS that EPS with negative charge or small size can act as mild stimulators of immune cells, whereas those polymers non-charged and with a large size present a suppressive profile (Alessandri et al. 2019).

Distinctive immunomodulatory properties of EPS including the promotion of IL-10 and Tregs endow it with great anti-allergic potential. Intranasal exposure to EPS of *Bifidobacterium longum* 35624 could modulate allergic responses in mice with OVA-induced respiratory allergy by reducing the accumulation of eosinophils in lung and the expression of Th2-related markers (CCL11, CCR3, IL-4, IL-13), and IL-10 secretion mediated by TLR2 was essential to reduce eosinophils and Th2 cytokines (Schiavi et al. 2018). Homoplastically, the protective effect of *Bacillus subtilis* on HDM-induced allergic eosinophilia in mice involved the production of EPS under the mechanism of that DCs treated with EPS diminished Th2 polarization and IL-5 production, preventing the development of eosinophilia (Swartzendruber et al. 2019). Notably, regulation of bacterial EPS on FA was also highlighted that gavage of EPS from *Bifidobacterium breve* WBBR04 could considerably decrease the serum IgE and cytokines (e.g., IL-4 and IL-5) to relieve OVA-induced FA, mainly through enhancing the intestinal barrier integrity and hence isolating the food allergens efficaciously (Luo et al. 2020). These evidences support the perspective that EPS could help modulate the immune system to the prevention or treatment of allergic diseases such as FA, and further studies are necessary to explore the relevant probiotic strains to produce EPS with high-efficiency anti-allergic activity and its immunoregulatory mechanisms.

Surface (S)-layer proteins

In addition to the common components on the cell wall or membrane of bacterial, the surface (S)-layer proteins (SLPs), wrapped in the outermost layer of bacteria and composed of protein or glycoprotein subunits that arranged in a regular lattice, also have various beneficial biological functions. There are presently more than ten species of *Lactobacillus* have been identified with SLPs. SLPs play a crucial role in the intestinal adhesion process of probiotics. The adhesion rate of *Lactobacillus acidophilus* to IECs was significantly reduced after SLPs deletion. *Lactobacillus* strains (*Lactobacillus helveticus* fb213, *Lactobacillus acidophilus* fb116 and fb214) with SLPs removal showed a significant decrease in the adhesion ability to HT-29 cells and reduced the survival of these strains in the gastrointestinal digestion compared to the intact *Lactobacilli* (Meng et al. 2014). Besides, SLPs could modulate the expression of TJs and regulate the inflammatory responses by inhibiting the activation of NF- κ B or MAPK signaling pathways, thus protecting the intestinal barrier (Acosta, Ruzal, and Cordo 2016; Zhang et al. 2018). Likewise, intervention of micro integral membrane protein, the smallest domain of SLPs from *Lactobacillus plantarum*, was found to regulate the expression level of anti- or pro-inflammatory cytokines through the inhibition of TLR4-related pathways and histone acetylation, enhancing the intestinal epithelial barrier and improving gut damage

induced by DSS (Yin et al. 2018). Notably, certain SLPs are also associated with the functional regulation of DCs and T cells. The surface (S)-layer A protein (SlpA) of *Lactobacillus acidophilus* NCFM was identified as a ligand of dendritic cell-specific intercellular adhesion molecule 3-grabbing non-integrin (DC-SIGN), the interaction of SlpA with DC-SIGN involved in a concentration-dependent IL-10 production and was crucial in priming T cells differentiation after the combination with LPS stimulation to DCs (Konstantinov et al. 2008).

Overall, the health benefits of SLPs are mainly including the enhancement of the survival of probiotics and adhesion to IECs, maintenance of intestinal barrier function, modulation of immune cells functions and regulation of inflammatory response. Although there are no direct evidences that SLPs can be involved in effective alleviation of FA, mechanically, SLPs have considerable potential to affect the development of FA through the aforementioned regulatory effects.

DNA

Bacterial DNA, especially containing unmethylated CpG motifs (CpG DNA), is another probiotic component with immunostimulatory properties and is recognized by TLR9 located mainly in endosomes preferentially. Upon activation by CpG DNA, TLR9 translocates to the tubular lysosomal compartment to bind with CpG DNA and initiates downstream signal cascades, such as MyD88 and JNK signaling pathways, inducing a robust Th1 immune response (Zhou and Deng 2021). CPG DNA or CpG oligodeoxyribonucleotides (ODNs) could induce the secretion of IFN- γ by natural killer (NK) cells, and directly stimulate DCs, macrophages and human PBMCs to produce IL-6, TNF- α and IL-12 (Zhou and Deng 2021). In addition, B cells stimulated by CpG ODNs trigger a rapid secretion of IL-6 and IL-10, and certain ODNs could induce the B cells differentiated into IgG-secretion instead of IgE-secretion plasma cells in a T cell-independent manner (Montamat et al. 2021; Zhou and Deng 2021). Notably, there are species and sequence specific differences in the recognition of TLR9 that a pair of tightly positioned CpG motifs within ODNs is indispensable to activate human TLR9, whereas an ODN with a single CpG motif is required for the effective activation of mouse TLR9 (Pohar et al. 2017).

Considering the properties of TLR9 activation inducing Th1-dominant response, TLR9-targeted strategies have emerged in the treatment of Th2-related atopic diseases and the efficacy have been demonstrated in allergic diseases such as asthma and FA (Iliev et al. 2008; Psallidas et al. 2021). *Bifidobacterium* and *Lactobacillus* (e.g., *Lactobacillus plantarum* and *Lactobacillus rhamnosus*) contain a high content of CpG motifs in the genomes, and the frequency of CpG motifs may affect the immunoregulatory properties of probiotics (Kant et al. 2014). Specifically, probiotics with abundant CpG DNA could better maintain the mucosal function and reverse the imbalance of Th1/Th2 responses due to the unique TTTCGTTT motif (Zhong et al. 2012). Genomic

DNA from the mixture of LGG and *Bifidobacterium longum* BB536 was demonstrated to significantly inhibit the OVA-induced allergic reaction with the comparable effects to that of living bacteria, promoting the Th1 response skewing, increasing the proportion of CD4⁺ CD25⁺ Tregs and improving the intestinal barrier function through TLR9/NF- κ B signal pathway (Zhong et al. 2012). Furthermore, the ODN BL07S, identified from genomic DNA of *Bifidobacterium longum* BB536, could also prevent allergic responses by increasing Th1 cytokines production, decreasing Th2 cytokines and OVA-specific IgE levels (Takahashi, Kitazawa, Iwabuchi, et al. 2006; Takahashi, Kitazawa, Shimosato, et al. 2006).

In addition to reversing the Th2 response bias via inducing Th1 immune response and promoting the differentiation of Tregs, recently, other mechanisms have been revealed for bacterial DNA to inhibit allergic diseases. Specific recognition of TLR9 to bacterial CpG DNA could induce the expansion of lung interstitial macrophages to prevent HDM-induced asthma through the production of IL-10 (Sabatel et al. 2017). Alternatively, activation of TLR9 by CpG A prompted NK cells to produce IFN- γ , which directly constrained the proliferation of ILC2 and production of Th2 cytokines through a signal transducer and activator of transcription 1-dependent mechanism, consequently alleviating IL-33-mediated airway inflammation (Thio et al. 2019). Collectively, immunostimulatory CpG is associated with the anti-allergy effects of probiotics and utilizing CpG-rich DNA in probiotics for immune responses regulation will be a promising strategy to prevent or treat FA.

Conclusion and perspectives

Therapeutic strategies targeting on the modulation of intestinal microbiome has been highlighted as the cutting-edge and highly effective approaches to solve FA. Multiple studies have confirmed that probiotics influence the development of FA via modulating the interaction of gut microbiome and immune system. The current mainstream viewpoints focus on the effects on the microbiota compositions and metabolites, while the efficacy of some inactivated probiotics suggests that we should also pay attention to the immunomodulatory effects of the probiotic components. These probiotic components could enhance the intestinal barrier function, increase the generation of Tregs and redress Th2-biased allergic reactions through promoting Th1 adaptive responses. Understanding the regulatory mechanisms will provide new insight for the resolution of FA and guidance for the development of probiotic products.

Probiotic components have complex structures, and not all components but those with specific structures exhibiting desired immunomodulatory activity can be utilized with anti-allergic potential. In addition, some components are often considered to be virulence factors such as flagellin and pili. Therefore, the applications of advanced separation techniques, structural characterization, multi-omics techniques such as lipidomics and proteomics are essential to discover the patterns of beneficial structures, which will

provide better insights into the contribution of probiotic interventions in the prevention and treatment of FA. From another perspective, genetic engineering such as CRISPR-based gene editing could be applied in probiotics improvement to eliminate undesired detrimental components and even endow new beneficial characteristics so as to exert the maximum immunomodulatory activity of probiotics. Besides, well-designed animal models and human intervention studies should be conducted to deeply understand the precise mechanisms of probiotic components in modulating FA and to support the effective applications of these components in the development of therapeutic strategies to manage FA.

Disclosure statement

The authors declare no conflict of interest.

Funding

This work was supported by the National Natural Science Foundation of China (31760431, 32072241), the Nutrition Scientific Research Foundation of BYHEALTH (TY202001031), and the Technology planning project of Jiangxi Provincial Health Commission (202210074).

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