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Targeting Food Allergy with Probiotics

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Abstract

The dramatic increase in food allergy prevalence and severity globally is demanding effective strategies. Food allergy derives from a defect in immune tolerance mechanisms. Immune tolerance is modulated by gut microbiota composition and function, and gut microbiota dysbiosis has been associated with the development of food allergy. Selected probiotic strains could act on immune tolerance mechanisms. The mechanisms are multiple and still not completely defined. Increasing evidence is providing useful information on the choice of optimal bacterial species/strains, dosage, and timing for intervention. The increased knowledge on the crucial role played by gut microbiota-derived metabolites, such as butyrate, is also opening the way to a post-biotic approach in the stimulation of immune tolerance.

Keywords

Butyrate · Cow's milk allergy · Gut microbiota · Immune tolerance · Post-biotics · Probiotics

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Abbreviations

BLG	β-lactoglobulin
CMA	cow's milk allergy
EHCF	extensively hydrolyzed casein formula
FA	food allergy
LAB	lactic acid bacteria
LGG	*Lactobacillus rhamnosus* GG
OIT	oral food immunotherapy
OVA	ovalbumin
PBMCs	peripheral blood mononuclear cells

SCFAs	short-chain fatty acids
SU	sustained unresponsiveness
Tregs	regulatory T cells

1 Introduction

Food allergy (FA) is "an adverse health effect arising from a specific immune response that occurs reproducibly" according to the 2010 National Institute of Allergy and Infectious Diseases, National Institutes of Health (NIAID/NIH)-supported Guidelines for the Diagnosis and Management of Food Allergy in the United States (Boyce et al. 2010). It is one of the most common allergic disorders in the pediatric age, and it has been recognized as a global health problem that affects millions of persons, particularly in developed countries. Studies have suggested that the natural history of FA has changed during the last two decades, with a dramatic rise in the prevalence, severity of clinical manifestations, and risk of persistence into later ages, leading to an increase in hospital admissions, medical visits, treatments, and burden of care on families and to an important economic impact, with significant direct costs for the families and healthcare system (Skripak et al. 2007; McBride et al. 2012; Gupta et al. 2013). In Europe, around seven million of people suffer from challenge-proven FA. If this prevalence is projected onto the world's population of seven billion, it translates into 63 million–1.16 billion of potential food-allergic people, with a greater incidence in children (5–8%) than in adults (1–2%) (Fiocchi et al. 2010). Furthermore, about 8% of people suffering from FA are exposed to the risk of potentially life-threatening allergic reaction resulting in death, mainly among children aged 0–14 years. According to the most recently available epidemiological data, time trend analysis showed up to sevenfold increase in hospital admissions for severe food-allergic reactions in children in the UK, USA, Italy, and Australia over the last 10 years (Berni Canani et al. 2013; Turner et al. 2015; Mullins et al. 2015; Nocerino et al. 2015; Mullins et al. 2016). Although more than 170 foods have been identified as triggers of FA, there is a rather short list of foods account for most of the more serious disease burden: namely peanuts, tree nuts, fish, shellfish, egg, milk, wheat, soy, and seeds, with national and geographical variations concerning the most common FA (Boyce et al. 2010; Sicherer et al. 2010; Ben-Shoshan et al. 2010; Chafen et al. 2010; Osborne et al. 2011; Gupta et al. 2011; National Academies of Sciences 2016).

Food allergy derives from a breakdown of immune tolerance. Current knowledge suggests that the development of FA might be influenced by genetics, environment, and genome-environment interactions, leading to immune system dysfunction, mediated at least in part by epigenetic mechanisms (Berni Canani et al. 2015; Paparo et al. 2018). Many factors have been postulated to contribute to the onset of FA. Among the multiple immutable risk factors that could influence FA onset, there are the male sex, the race/ethnicity (increased risk among Asian and black children compared with white children), and genetics (familial associations, HLA, and specific genes) (National Academies of Sciences 2016; Sicherer et al. 2017; Allen and Koplin 2016; du Toit et al. 2016; Hong et al. 2015; Gupta et al. 2016). In addition, there are other risk factors that can be addressed to potentially reduce/prevent FA, such as atopic disease manifestations (comorbid atopic dermatitis), increased hygiene, vitamin D insufficiency, dietary fat (reduced consumption of omega-3-polyunsaturated fatty acids), reduced consumption of antioxidants, increased use of antacids (that reduce digestion of allergens), obesity, the timing and route of exposure to foods (increased risk for delaying oral ingestion of allergens with environmental exposure in the absence of oral exposure leading to sensitization and allergy), and in particular the influence of the microbiome (Savage et al. 2018; Huang et al. 2017; Sicherer et al. 2010). There is mounting evidence that the alterations of microbiota composition early in life play a key role in early host immunological development and represent a critical factor underlying FA (Prince et al. 2015). Fig. 1 summarizes the main possible

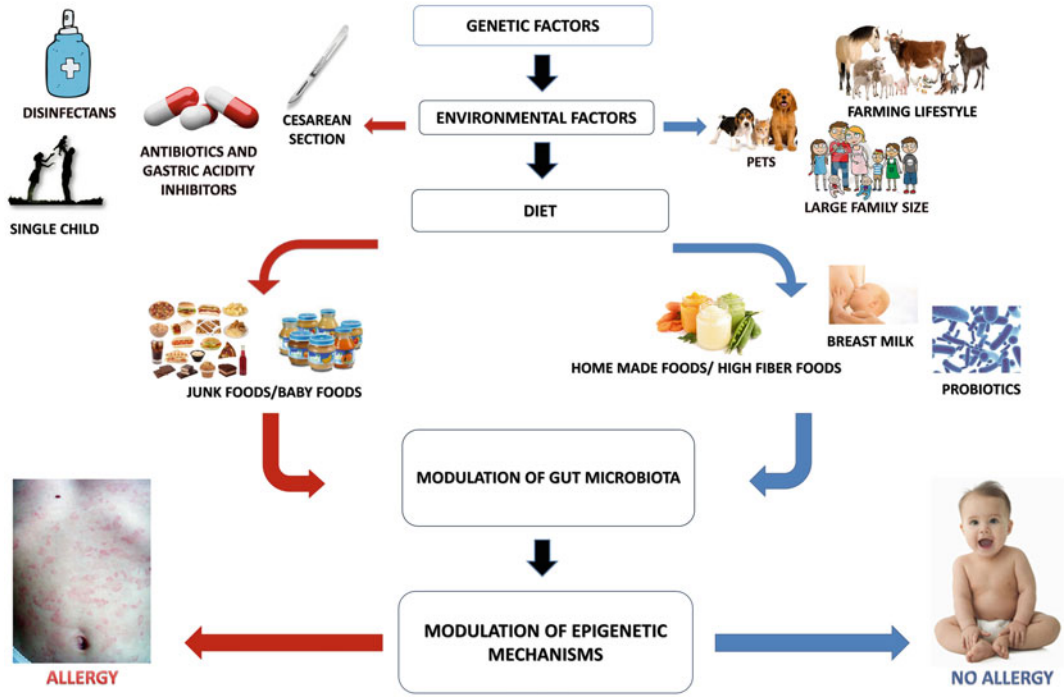

Fig. 1 Gut microbiota as a target of intervention against allergy. Several environmental and dietary factors could modulate the diet-microbiota-epigenetics axis influencing the occurrence of food allergy. On the left side of the figure are summarized the most relevant factors able to increase the risk of food allergy (red arrows), whereas on the right side of the figure are reported the most beneficial factors able to protect the baby against the occurrence of food allergy (blue arrows)

contributing factors that have been ascribed to FA development. Many subjects with FA will naturally outgrow it over time; however, the natural course highly depends on the causative allergen. For example, cow's milk allergy (CMA) usually resolves in more than 50% of children by age 5–10 years, hen's egg allergy approximately resolves in 50% of children by age 5–10 years, and 50% of children with wheat allergy outgrow by age 7 years. Other FAs (peanut, tree nut, fish) have low rates of resolution or are considered persistent (Savage et al. 2016). There is no Food and Drug Administration (FDA)-approved treatment for FA, and the current standard of care is the strict and careful dietary avoidance of the offending food allergens with the risk of nutritional deficiencies. In addition, the risks of accidental ingestion are relatively common, and the prompt treatment of symptoms with antihistamines, glucocorticoids, or epinephrine in case of systemic reactions is advocated. All these factors contribute to anxiety and stress and significantly affect the quality of life of patients and their families (Burks et al. 2018; Sicherer and Sampson 2018; Heine 2018). However, in the past 10 years, a significant amount of emerging therapies for FA have been addressed. These therapeutic strategies are focused on reducing levels of allergen-specific IgE, enhancing levels of allergen-specific IgG or IgA, suppressing Th2 effector cells, or enhancing regulatory T cells through a variety of allergen-specific and allergen non-specific strategies (Berin 2014). The main new therapeutic perspectives for the treatment of FA include allergen-specific (oral, sublingual, epicutaneous, subcutaneous immunotherapy and heat treatment of food) and non-allergen-specific therapies (humanized monoclonal antibodies, anti-IgE and anti-IL5, probiotics). Allergen-specific therapies are successful to variable

degrees in achieving desensitization, defined as increased threshold for reaction to food allergen, with regular exposition to the allergen. On the other hand, to date, none of these experimental therapies have been shown to lead to permanent tolerance or cure, defined as the absence of symptoms after ingestion of the food allergen ad libitum even after prolonged periods of avoidance, and safety remains a major concern (Burks et al. 2018; Rachid et al. 2018). Recent data are focused also on heat treatment of food, with the modifications of allergen structure to reduce IgE binding. The introduction of extensively heated milk and egg protein into the diet of subjects with milk and egg allergy who tolerate the baked form, rather than strict avoidance, is becoming an alternative approach to induce a faster acquisition of immune tolerance (about 10 times more likely to outgrow allergy comparing to those who strictly avoid allergen), with changes in immune parameters (increase in IgG4 and decrease in allergen-specific IgE) (Wood et al. 2013; Sicherer et al. 2014). Heating to reduce allergenicity is not applicable to antigens such as peanut, where high heat increases allergenicity rather than reducing it. In this case, allergens can be also modified through digestion, which forms peptides that are too short to cross-link IgE but maintain T cell epitopes that would have the capacity to generate T cell-mediated immunomodulation (Ramesh et al. 2016). However, all these strategies present several pitfalls and uncertainties: optimal dose, frequency and duration, adverse events, potential for onset of eosinophilic esophagitis, achieving of desensitization but not immunological tolerance, and long-term efficacy. Thus, their precise role in the management of FA has yet to be determined (Rachid et al. 2018). Among the non-allergen-specific therapies, the more promising approach for FA treatment is the use of probiotics, defined as live microorganisms that when consumed in adequate amounts as part of food or as oral supplements confer a health benefit on the host (Hill et al. 2014). Probiotics actions are mainly mediated via the innate immune system (toll-like receptors), resulting in the promotion of T helper 1 differentiation, production of regulatory cytokines (IL-10 and TGF-beta), and enhanced intestinal IgA responses (Rautava et al. 2012). The effects can vary widely, depending on the probiotic strain, dose, timing, and food matrix used (Heine 2018). This therapeutic strategy represents attempt to deliberately modify the microbiota and their metabolism, with the idea that manipulating microbial communities to the host's advantages could treat FA (Ho and Bunyavanich 2018). This review is focused on the preclinical and clinical evidence on the role of probiotics in preventing or treating FA.

2 Main Preclinical Evidence on the Probiotics Efficacy in Food Allergy

Immune tolerance is the most important therapeutic target in FA. Immune tolerance is modulated by the activity of a well-modulated network composed by several immune and nonimmune mechanisms. Gut microbiota and its metabolites (mainly the short-chain fatty acid, butyrate) exert a pivotal role in immune tolerance. Main preclinical evidence on the probiotics activity against FA are summarized in Table 1. Evidence support the concept that probiotics could act at different level on immune tolerance network in FA: modulating gut microbiota composition and function (increased production of butyrate (Berni Canani et al. 2016) and interacting with enterocytes with subsequent modulation of nonimmune (gut permeability and mucus thickness) (Sudo et al. 1997; Sütas et al. 1996; Malin et al. 1997) and immune tolerogenic mechanisms (stimulation of sIgA and beta-defensins production) (Hardy et al. 2013) and modulation of cytokines response by immune cells (Kim et al. 2008; Torii et al. 2007; Maassen et al. 2000; Niers et al. 2005; Takahashi et al. 2006a, b). In vitro stimulation of human peripheral blood mononuclear cells (PBMCs) with selected probiotic strains is a commonly used experimental tool for the investigation of the effect of these microorganisms on immune cells. The incubation of PBMCs with lactic acid bacteria (LAB) strains such as *Lactobacillus plantarum* (*L. plantarum)* and *Bifidobacterium adolescentis (B. adolescentis*) resulted in an

Table 1 Main preclinical evidences on the probiotics role against food allergy

Biological effects	Bacterial strains	References
Intestinal barrier maturation	*Bifidobacterium lactis/bifidum*	Sudo et al. (1997)
	Lactobacillus rhamnosus GG	Sütas et al. (1996)
		Malin et al. (1997)
Immune response modulation Th1/Th2 balance: Th1 production	*Bifidobacterium lactis/bifidum*	Kim et al. (2008)
	Lactobacillus acidophilus/ reuteri	
	Lactobacillus rhamnosus GG	Torii et al. (2007)
		Maassen et al. (2000)
Immune response modulation Th1/Th2 balance: Th2 suppression	*Bifidobacterium bifidum/infantis/ longum*	Niers et al. (2005)
	Lactobacillus acidophilus/ reuteri	
	Lactobacillus rhamnosus GG	Takahashi et al. (2006a, b)
		Kim et al. (2008)
		Aitoro et al. (2017a, b)
Immune system regulation: regulatory T (Treg) cell development	*Bifidobacterium bifidum/infantis/ lactis*	Niers et al. (2005)
	Lactobacillus acidophilus/ reuteri/casei *Lactobacillus rhamnosus GG*	Maassen et al. (2000)
		Kim et al. (2008)
		Smits et al. (2005)
Immune system regulation: tolerogenic dendritic cell development	*Bifidobacterium bifidum*	Niers et al. (2005)
	Lactobacillus reuteri/casei	
	Lactobacillus rhamnosus GG	Mohamadzadeh et al. (2005)
		Braat et al. (2004)
		Smits et al. (2005)
Immunomodulation: suppression of IgE production	*Bifidobacterium bifidum/longum*	Kim et al. (2008)
	Bifidobacterium lactis Bb-12	
	Lactobacillus acidophilus	Takahashi et al. (2006a, b)
	Lactobacillus rhamnosus GG	Borthakur et al. (2008)
		Borchers et al. (2002)
		Torii et al. (2007)
Epigenetic modulation of TH1/Th2 genes expression	*Bifidobacterium breve*	Ghadimi et al. (2012)
	Lactobacillus rhamnosus GG	

increase in the production of the regulatory cytokine IL-10 by monocytes and dendritic cells and to an enhance of IFN-γ production by T cells (Cross and Gill 2001; Karlsson et al. 2004, Mohamadzadeh et al. 2005). The addition of probiotics mixture (*L. acidophilus* W55, *L. casei* W56, *L. salivarius* W57, *L. lactis* W58, *B. infantis* W52, *B. lactis* W18, and *B. longum* W51) to PBMCs from children with FA resulted in increased T cell proliferation with enhanced production of Th1 and regulatory cytokines (Flinterman et al. 2007). An increase in T and B cell proliferation and a reduction in IgE production were also observed in PBMCs from children with FA treated for 3 months with the same probiotic mixture (Flinterman et al. 2007). Using a 3D co-culture model of intestinal epithelial cells and PBMCs as an in vitro model of the intestinal mucosal immune system, Ghadimi et al. demonstrated that a commensal probiotics *B. breve* and *L. rhamnosus* GG (LGG) inhibit activation of inflammatory IL-23 and IL-17 cytokines, thereby reducing histone acetylation and simultaneously enhancing DNA

methylation (Ghadimi et al. 2012). The limitation of studying the effect of probiotics in vitro lies in the extrapolation of the results to in vivo benefits. For that reason, another commonly used experimental toll in this area is based on the use of animal model of FA. Differential effects in relation to molecular action of oral administration of three LAB strains (*B. coagulans* 09.712 (Bc), *L. plantarum* 08.923 (Lp), and *B. infantis* 11.322) in alleviating Th2-driven intestinal inflammation and other symptoms associated with food-induced anaphylaxis were demonstrated in a murine model induced by a major shrimp allergen, ST. In particular, oral supplementation with Bc and Lp significantly ameliorates anaphylaxis symptoms and increases the population of CD4 + FoxP3+ T cells in ST-sensitized mice through mTORC inhibition, FoxP3 upregulation, and GATA-3 downregulation (Linglin et al. 2017). Zang et al. investigated the preventive and therapeutic effects of oral *C. butyricum* on anaphylactic symptoms in FA mice model induced by a β-lactoglobulin (BLG) as allergen, a well-established model of CMA. The authors observed that the oral treatment with *C. butyricum* significantly ameliorated anaphylaxis symptoms and increased sIgA and CD4+ CD25+ FoxP3Treg cell in the spleen from BLG-sensitized mice (Juan et al. 2017). Neonatal monocolonization of germ-free mice by *L. casei* BL23 modulated the allergic sensitization to cow's milk proteins, developed higher IgG responses against caseins, and elicited by *L. casei* that was able to hydrolyze insoluble caseins into soluble immunogenic peptides (Maiga et al. 2017). Using ovalbumin (OVA)-sensitized murine model, it was demonstrated that oral administration of *B. infantis* ameliorated allergic symptoms, including reducing OVA-specific IgE and IgG1 levels in the serum and Th2 cytokines release in the spleen. Moreover, gut microbiota analysis showed that the probiotics-mediated protection was conferred by upregulation of the relative abundance of *Coprococcus* and *Rikenella* at genus level (Yang et al. 2017). Similar results were obtained by others that observed a decrease of concentrations of IgE, IL-4, and IL-13 following administration of *B. infantis* CGMCC313–2 in BLG-sensitized mice (Meng-Yun et al. 2017). Oral administration of VSL#3 to sensitized mice significantly reduces Th2 immune responses and protects against anaphylactic reactions induced by the allergen in a mouse model of FA. Also, the incubation of mouse spleen cells from sensitized mice with probiotic mixture reduced allergen-stimulated IL-5 and IL-13 production and increased of IFN-γ and IL-10 production (Schiavi et al. 2011). An immunoregulatory action by LGG has been demonstrated in a murine model of CMA. LGG administration was able to suppress of Th2 responses such as reduced hypersensitivity scores and lowered serum cow's milk protein (CMP)-specific IgG1 while promoting Th1 responses by causing elevated IFN-γ and CMP-specific IgG2a levels (Thang et al. 2011). Similar results have been reported by our group in a BLG-sensitized mice model, in which we found that the administration of extensively hydrolyzed casein formula plus LGG elicited a significant reduction of allergic reaction and of IL-4, IL-5, IL-13, and specific IgE production (Aitoro et al. 2017a, b). The studies of probiotic strain-specific modulation on gut microbiota should be considered as a key channel that could affect its in vivo action. A strain-specific effect of different probiotic strains could be associated with a different impact on gut microbiota as demonstrated by Wang et al. (Wang et al. 2015). Instead, oral application of any LAB strains seemed to have no significant effect on the overall gut microbiota structure, but the amount of specific species exerted notable changes (Ai et al. 2016).

Additional potential mechanisms by which probiotics exert pro-tolerogenic effects in the gut are related to the production of immunoregulatory metabolites, which interact with the host immune cells to promote non-responsiveness to innocuous luminal antigens (Nowak-Wegrzyn and Chatchatee 2017; Di Costanzo et al. 2016). Probiotics ferment fiber to short-chain fatty acids (SCFAs): butyrate, acetate, and propionate. Evidence suggests that SCFAs, particularly butyrate, contribute to mucosal homeostasis through the induction of Tregs and the regulation of epithelial barrier integrity (Berni Canani et al. 2015). Butyrate deficiency has been observed in allergic patients (Sandin et al. 2009; Berni Canani et al. 2016). It is possible to hypothesize that different

type of dysbiosis could lead to similar effects in term of SCFAs or of other microbiota-derived metabolites production that could facilitate the occurrence of allergy. Clostridia species belonging to cluster IV and XIVa are the prominent source of SCFAs in the colon. Bacteria-produced SCFAs have been implicated in the regulation of both the proportions and functional capabilities of Tregs in the colon (Arpaia and Campbell 2013; Smith and Howitt 2013), which, in some studies, has been specifically attributed to butyrate production by spore-forming *Clostridiales* (Furusawa and Obata 2013). SCFAs bind metabolite-sensing G-protein-coupled receptors (GPCRs) GPR43, GPR 109A, and GPR41 with varying affinities. These GPCRs are expressed on epithelial cells and immune cells. SCFAs activate GPCRs that stimulate colonic dendritic cells and macrophages to secrete IL-10 and promote development of Tregs in the mesenteric lymph nodes. Tregs are a source of tolerogenic cytokines, such as IL-10 and TGF-β that inhibit allergic and inflammatory responses. Tan et al. showed that dietary fiber/SCFAs together with vitamin A and a healthy gut microbiota maintain a tolerogenic mucosal environment and protect against the development of FA. This is achieved principally through enhancement of the tolerogenic CD103+ dendritic cells function, leading to increased Tregs differentiation. In addition, mice lacking GPR43 or GPR109A receptors for SCFAs showed exacerbated FA and fewer CD103 + dendritic cells (Tan et al. 2016). Data from our laboratory showed that oral butyrate treatment induces a dramatic inhibition of acute allergic skin response, anaphylactic symptom score, body temperature decrease, intestinal permeability increase, and anti-BLG-IgE, IL-4, and IL-10 production in a murine model of CMA, suggesting a protective role of butyrate against FA (Aitoro et al. 2017a, b). The mechanisms of action of butyrate are multiple; many of these involve an epigenetic regulation of gene expression through the inhibition of histone deacetylase (HDAC). The inhibition of HDAC 9 and 6 increases FoxP3 gene expression, as well as the production and suppressive function of Tregs (Tao and de Zoeten 2007). We evaluated the direct effects of butyrate on peripheral blood mononuclear cells (PBMCs) from children affected by challenge-proven IgE-mediated CMA. PBMCs were stimulated with BLG in the presence or absence of butyrate. Preliminary results showed that butyrate stimulates IL-10 and IFN-γ production and decreases DNA methylation rate of these two cytokines. Same effective butyrate dose induces FoxP3 promoter region demethylation and HDAC6/HDAC9 expression downregulation. The identification of bacterial metabolites, that affect positively the immune tolerance network, may be an interesting strategy against FA using a post-biotic approach.

3 Main Clinical Evidences on the Probiotics Efficacy in Food Allergy

The increasing evidence on the importance of the composition of the gut microbiota in the pathogenesis of FA supports clinical research on the potential role of the probiotics against these conditions. In this light, several studies have revealed the efficacy of selected probiotic strains against FA. The effect appears strain specific and more evident in the pediatric age. Thus, in a randomized double-blind placebo-controlled trial, it has been demonstrated that the administration of *L. casei* CRL431 and *B. lactis* BB12 added to hypoallergenic formula for 12 months did not affect the acquisition of immune tolerance to cow's milk proteins in infants with CMA (Hol et al. 2008). Whereas using a similar study design, we have demonstrated that the addition of the probiotic LGG to the extensively hydrolyzed casein formula (EHCF) is able to accelerate immune tolerance acquisition in infants with CMA. Infants (aged 1–12 months), consecutively referred for suspected CMA (IgE- or non-IgE-mediated) but still receiving cow's milk proteins, were invited to participate in the study. Subjects were randomly allocated to one of the two groups of dietary interventions: control group, received an EHCF, and active group, received an EHCF containing LGG (at least 1.4×10^7 CFU/100 mL). After 12 months, the double-blind placebo-controlled food challenge was negative in 15 of 28 control infants (53.6%)

and in 22 of 27 infants receiving EHCF with LGG (81.5%, $p = 0.027$) (Berni Canani et al. 2012a, b). The results were confirmed in a subsequent trial, when the effect of five different dietary strategies was investigated: EHCF, EHCF + LGG, partially hydrolyzed rice formula, soy formula, or amino acid-based formula, in children affected by IgE- or non-IgE-mediated CMA. After the treatment period of 12 months, the proportion of children acquiring tolerance to cow's milk proteins was significantly higher in the group receiving EHCF + LGG (78.9%) than in other groups (Berni Canani et al. 2013). At the 3-year follow-up of another pediatric cohort, a further confirmation of a greater rate of resolution of IgE-mediated CMA as well as a lower incidence of other atopic manifestations was described after treatment with EHCF+LGG (Berni Canani et al. 2017). These effects could derive at least in part by a modulation elicited by selected LGG components on immune functions through different pathways including enterocytes, monocytes, mast cells, DCs, and Tregs (Berni Canani et al. 2013; Pan et al. 2010; Ghadimi et al. 2008; Donato et al. 2010; Mileti et al. 2009) and by an expansion of butyrate-producing gut microbiota (Berni Canani et al. 2016). Accordingly, studies in infants with eczema and/or CMA who received EHCF supplemented with LGG showed benefits in decreasing gastrointestinal symptoms and inflammation (Isolauri et al. 2000; Baldassarre et al. 2010). Ingestion of LGG for periods ranging from 4 to 12 weeks has been associated with significant decreases in atopic dermatitis score compared with placebo in some small studies, but not in several more recent and larger trials (Wu et al. 2017). Others were unable to detect significant differences in the group overall but found the LGG-associated improvements to be significant in subgroups of children with IgE-associated disease (Viljanen et al. 2005). The combination of four probiotics (LGG, *L. rhamnosus* LC705, *B. breve* Bb99, and *Propionibacterium freudenreichii* ssp. *shermanii*) given in association with a prebiotic (galactooligosaccharides) reduced the incidence of eczema and atopic eczema and tended to reduce IgE-associated diseases overall in a primary prevention trial (Kukkonen et al. 2007). The same combination without prebiotic did not have a significant effect (Viljanen et al. 2005). The addition of prebiotic may have been the decisive difference, although clear evidence of its bifidogenic effect is still lacking.

Probiotics have been also proposed to reinforce the effectiveness of immunotherapy (Rachid and Keet 2018). Oral food immunotherapy (OIT) is currently the most investigated approach for persistent FA, and it is based on the concept that repeated oral/intestinal exposures to antigens normally lead to tolerance. Tang et al. performed a randomized double-blind placebo-controlled trial with the probiotic *L. rhamnosus* CGMCC 1.3724 and peanut OIT (PPOIT) in 62 children with peanut allergy. Subjects received a fixed dose of probiotic (or placebo) together with peanut OIT (or placebo) once daily for a total of 18 months. Sustained unresponsiveness (SU), determined by DBPCFC conducted 2–5 weeks after discontinuation of treatment, was achieved in 82.1% of patients receiving PPOIT compared with 3.6% of those receiving placebo, the highest rate of SU reported for any food immunotherapy treatment evaluated in a randomized controlled study to date. PPOIT also induced high rates of desensitization (90%) and was associated with reduced peanut skin test reactivity, decreased peanut-specific IgE, and increased peanut-specific IgG4 levels. PPOIT was well tolerated with no participants withdrawing because of adverse reactions (six participants withdrew for reasons unrelated to PPOIT treatment); this is in stark contrast to OIT whereby 10–30% of participants withdraw because of adverse reactions. At approximately 4 years after the study ended, 67% were still consuming peanut, and only 58% of the 12 participants who stopped peanut ingestion for 8 weeks demonstrated sustained unresponsiveness. Importantly, no OIT control group was evaluated to determine if the probiotic itself had any effect on SU (Tang et al. 2015). Further studies comparing peanut OIT with probiotic with peanut OIT with placebo will be required to evaluate this further.

4 Conclusions

Gut microbiota dysbiosis early in life could be a critical factor affecting the development of FA. Studies are promising, but more data are needed to support a wide use of probiotics against FA. Currently there are no positive recommendations from any scientific society to use specific probiotic strains for the prevention or treatment of FA. But, understanding how probiotics could influence gut bacteria communities and the immune system is opening the way to novel preventive and therapeutic strategies for FA. At this point, we need:

- More data on gut microbiota dysbiosis in children with allergic diseases.
- More data to determine whether changes in gut microbiota can occur as a result of probiotic therapy
- More data on the mechanisms of action elicited by selected probiotics against food allergy.
- Further studies to define optimal dose, timing, and combination of agents, as well as the optimal patient populations to achieve beneficial effects
- Replication of the promising results in collaborative well-designed multicenter studies with multidisciplinary expertise in pediatrics, gastroenterology, immunology, allergy, and microbiology

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