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Gut Microbiome as Target for Innovative Strategies Against Food Allergy

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The dramatic increase in food allergy prevalence and severity globally requires effective strategies. Food allergy derives from a defect in immune tolerance mechanisms. Immune tolerance is modulated by gut microbiota function and structure, and microbiome alterations (dysbiosis) have a pivotal role in the development of food allergy. Environmental factors, including a low-fiber/high-fat diet, cesarean delivery, antiseptic agents, lack of breastfeeding, and drugs can induce gut microbiome dysbiosis, and have been associated with food allergy. New experimental tools and technologies have provided information regarding the role of metabolites generated from dietary nutrients and selected probiotic strains that could act on immune tolerance mechanisms. The mechanisms are multiple and still not completely defined. Increasing evidence has provided useful information on optimal bacterial species/strains, dosage, and timing for intervention. The increased knowledge of the crucial role played by nutrients and gut microbiota-derived metabolites is opening the way to a post-biotic approach in the stimulation of immune tolerance through epigenetic regulation. This review focused on the potential role of gut microbiome as the target for innovative strategies against food allergy.

Keywords: immune tolerance, gut microbiota, mediterranean diet, dysbiosis, probiotics, gut microbiota metabolites, short chain fatty acids, butyrate

INTRODUCTION

The Changing Scenario of Food Allergy

Food allergy (FA) is one of the most common allergic disorders in the pediatric age, and it has been considered as a global health problem, particularly in industrialized world (1). During the last two decades, studies have suggested that the epidemiology of FA has shown a dramatic increase in the prevalence, severity of clinical manifestations and risk of persistence into later ages, leading to an increase in medical visits, hospital admissions, treatments, burden of care on families, and economic impact, with an increase of costs for the families and healthcare system (2–4). According to the most recent epidemiological data, time trend analysis showed up to a 7-fold increase in hospital admissions for food severe allergic reactions in children in the

UK, USA, Italy and Australia over the last 10 years (5–10). More than 170 foods have been identified as triggers of FA, such as tree nuts, eggs, peanuts, fish, shellfish, milk, wheat, soy, and seeds, with national and geographical variations concerning the most common FA (1, 10–15).

New Insights in the Pathogenesis of FA

FA derives from a breakdown of immune tolerance to dietary antigens (16). Immune tolerance mechanisms involved the activation of dietary antigens specific regulatory T cell (Tregs) (17). Current knowledge suggests that the epidemiology of FA may be influenced by epigenome-genome-environment interactions leading to an alteration of immune system function (18, 19). To stabilize or fall the prevalence of FA, new and innovative strategies to reduce FA incidence are required. Many factors have been postulated to contribute to the onset of FA. The multiple immutable risk factors that could influence FA onset include male sex, ethnicity (increased risk among Asian and African Americans children), and genetics (familial risk, human leukocyte antigen (HLA), and specific genes) (2, 20–25). In addition, there are other modifiable factors that can be potentially targeted to reduce or prevent FA. These factors are related (mode of delivery, breast milk, use of antibiotics or gastric acidity inhibitors, use of antiseptic agents, rural environment, junk food-based and/or low-fiber/high-fat diet, consumption of unpasteurized milk or fermented foods, exposure to pets), or unrelated (comorbid atopic dermatitis, timing and route of exposure to foods, reduced consumption of omega-3-polyunsaturated fatty acids or vitamin D insufficiency, antioxidants,) to an influence on gut microbiome development and function (26–40) (**Figure 1**).

Clinical Consequences of Gut Microbiome Dysbiosis in Children With FA

Many subjects with FA naturally outgrow it over time. Cow's milk allergy (CMA), hen's egg allergy and wheat allergy resolve in ∼50% of children by the age of 5–10 years. Other FAs (including peanuts, tree nuts, fish) have low rates of resolution and are considered persistent (41). In addition, many forms of FA, may be related with later development of other allergic manifestations such as oculorhinitis, atopic dermatitis, asthma, and urticaria (the so called "Atopic March") (42), as well as other diseases such as functional gastrointestinal disorders (FGIDs) (30, 43), inflammatory bowel diseases (IBD) (44), and psychiatric disorders, such as autistic spectrum disorders (ASD) attention deficit hyperactivity disorder (ADHD), and obsessive-compulsive disorder (OCD) (45). The pathogenesis of these events is still largely unknown, but increasing evidence suggest the hypothesis that a perturbation of gut microbiome, leading to alterations in immune system and gut-brain axis, could influence the occurrence of FA and FA-related conditions later in life (**Figure 2**).

Abbreviations: FA, food allergy; CMA, cow's milk allergy; EHCF, extensively hydrolyzed casein formula; LGG, *Lactobacillus rhamnosus* GG; OIT, oral food immunotherapy; SU, sustained unresponsiveness; PBMCs, peripheral blood mononuclear cells; BLG, β lactoglobulin; OVA, ovalbumin; LAB, lactic acid bacteria; NDC, Non-digestible dietary carbohydrates; SCFAs, short chain fatty acids; Tregs, regulatory T cells; DCs, dendritic cells; Kyn, kynurenine; AhR, arylhydrocarbonreceptor; IPA, indole 3-propionic acid; I3A: indole-3-aldehyde; I3C, indole-3-carbinole.

Gut Microbiome Features in FA

Investigating the Metagenomic and Metabolomics Features of Gut Microbiome

The knowledge and awareness of the roles played by gut microbiome and metabolites in the balance between health and disease is rapidly increasing. This is mainly due to advances in technology and the availability of high-sensitivity means to study microbial communities in any type of ecosystem. It is important for the clinicians and researchers dedicated to the FA field to know potential and limits of these technologies to better understand the value and significance of the findings reported in literature. **Box 1** summarizes terminology for gut microbiota-based investigations in FA.

Due to the power of genome DNA sequencing, we have learned much about the composition of gut microbial communities. In addition, the potential of transcriptomics, proteomics, and metabolomics are enlarging our understanding of the gut microbiota role in human health. Until the 1990s, knowledge of the gut microbiome was limited because the structure of gut microbiota was characterized using bacteriological culture. In the last decade, the composition of the gut microbiota was described by next generation sequencing of 16S ribosomal RNA genes. This is increasing the amount of information that can be retrieved by studying metagenomes from human samples, with the capability to infer the abundance of genes and potential metabolic pathways that characterize a microbial community. It is possible to describe the taxonomic composition of the microbiota and also to study the potential functions in a given system. Such methodological background is fundamental to investigate associations between microbiota structure and health as well as other environmental factors (46) and also to observe the changes of the gut microbiota in response to disease or perturbations in diet or lifestyle. An advanced technique to investigate gut microbiota at deep level is shotgun sequencing that represents a massive sequencing of the whole genome. Shotgun sequencing involves DNA random fragmentation, sequencing of these fragments and reconstruction of overlapping sequences to assemble them into a continuous sequence (47). Metabolomics represents one of the meta-omic approaches to study gut microbiota functions. Metabolomics uses high throughput techniques to characterize and quantify small molecules in several biofluids, such as feces, urine, plasma, serum, and saliva (48). The use of metabolomics is considered a powerful top-down systems biology approach, and it is essential to reveal the genetic-environment-health relationship, as well as the clinical biomarkers of diseases (49). Currently, the rapid development of several analytical platform, including liquid chromatography (LC), gas chromatography mass spectrometry (GC- MS), high-pressure LC (HPLC), ultra-pressure LC (UPLC), electrophoresis (CE) coupled to mass spectrometry (MS), Fourier transform infrared spectroscopy (FTIR), ion cyclotrone resonance-FT (ICR-FT), capillary and nuclear, and proton nuclear magnetic resonance spectroscopy (NMR-1H-NMR),

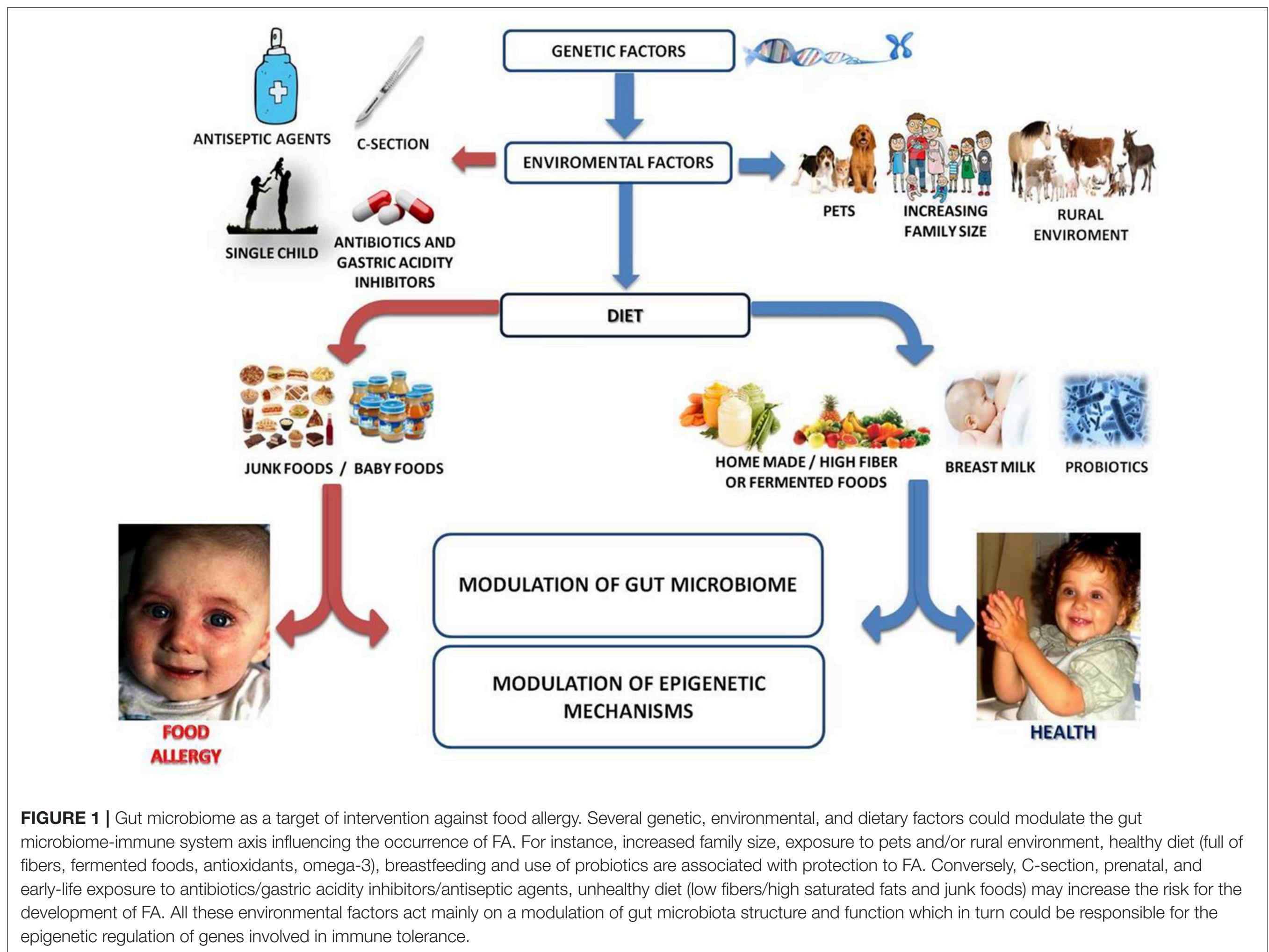

FIGURE 1 | Gut microbiome as a target of intervention against food allergy. Several genetic, environmental, and dietary factors could modulate the gut microbiome-immune system axis influencing the occurrence of FA. For instance, increased family size, exposure to pets and/or rural environment, healthy diet (full of fibers, fermented foods, antioxidants, omega-3), breastfeeding and use of probiotics are associated with protection to FA. Conversely, C-section, prenatal, and early-life exposure to antibiotics/gastric acidity inhibitors/antiseptic agents, unhealthy diet (low fibers/high saturated fats and junk foods) may increase the risk for the development of FA. All these environmental factors act mainly on a modulation of gut microbiota structure and function which in turn could be responsible for the epigenetic regulation of genes involved in immune tolerance.

allowed to better define bacteria related-metabolites and their metabolic pathways (50). **Box 2** summarizes techniques used to investigate the gut microbiota metagenomic and metabolomic features. Gut microbiota metabolomic features are still largely unexplored. Metabolomics will provide important insides in the pathogenesis of FA. In this light, preliminary data available on short chain fatty acids (SCFA) profile are opening new perspective of intervention (see below). What is needed is a transition from descriptive research to understanding the ways the microbiome interacts with the host and plays a role in health and disease. In this frame, controlled clinical interventions are of utmost importance to establish microbiota causative involvement and are the basis to implement approaches of personalized medicine (51, 52). The study of the relationship between microbiome and FA may begin with association and be translated to causation and clinical practice with appropriate advances in knowledge. Wide screening of microbial diversity in gut microbiome of patients with a sure diagnosis of FA, including a well-matched control population, may identify useful signatures in the microbiome that are specific for certain types of FA (53). If the wide screening included cohorts of patients with different dietary style or ethnicity, the common microbial signatures would be even stronger and provide a solid indication of the microbial biomarkers of FA. Further mapping of the genomic features associated with FA may be inferred by metagenomics and metabolomics, which may provide information on the functional microbial signatures associated with FA.

Biomarker strains or defined microbial systems may be tested in gnotobiotic or humanized animal models to observe the development of the disease, and beneficial vs. detrimental microbial metabolites can be recognized and used as final targets of microbiome-targeted personalized interventions. The identification of bacterial metabolites that positively affect the immune tolerance network, may be an interesting strategy against FA using a post-biotic approach.

Evidence on Gut Microbiome Dysbiosis in FA

Mounting evidence indicates that gut microbiome dysbiosis early in life represents a critical factor underlying FA (26, 27, 54, 55). Experimental data from animal models suggest a link between gut microbiome and the occurrence of FA. Tregs was found reduced in mice treated with antibiotic or

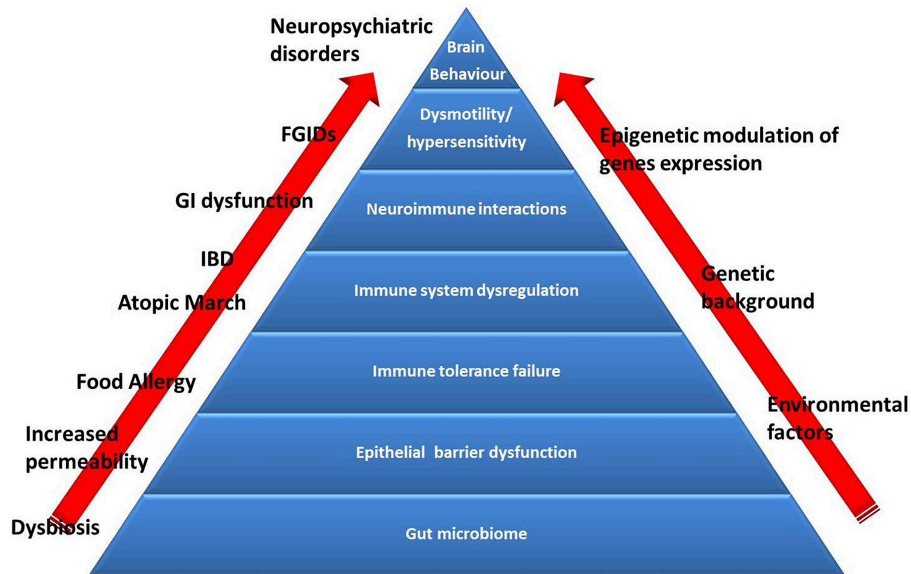

FIGURE 2 | The Food Allergy pyramid. Children with FA present an increased risk to develop other conditions such as allergic disorders (atopic march), inflammatory bowel diseases (IBD), functional gastrointestinal disorders (FGIDs), and neuropsychiatric disorders. Several genetic factors are implicated in the pathogenesis of these conditions, but recent evidence suggest the pivotal role of gut microbiome dysbiosis (induced by environmental factors). Emerging evidence support the hypothesis of dysbiosis as the first hit in the development of alterations in intestinal barrier and immune system function (responsible for the occurrence of FA and atopic march) and dysregulation of the brain-gut endocrine-immune system axis (responsible for the occurrence of FGIDs, IBD, and neuropsychiatric disorders), at least in part through an activation of epigenetic mechanisms.

Box 1 | A brief glossary for a better understanding of the potential of gut microbiota as target against food allergy.

Microbiota	The community of microbes in a particular ecosystem
Microbiome	The sum of micro-organisms, and their total genome capacity, in a particular environment
Operational taxonomic unit	A clusters of micro-organisms, grouped by DNA sequence similarity of a specific taxonomic marker gene. Operational taxonomic units are defined based on the similarity threshold (usually 97% similarity) set by the researcher
Microbiota diversity	A measure of how many different species are distributed in the community
Eubiosis	Healthy balance in a microbial ecosystem
Dysbiosis	A state of imbalance in a microbial ecosystem
Metagenomics	The study of the metagenome; the metagenome is the collective assembly of genomes from an environment (for example, the gut)
Metabolomics	The study of the metabolome; the metabolome is the collective array of metabolites present in a biological sample

in *germ free* mice, with consequent predisposition to allergy development (56–58). Administration of defined Clostridia, or bacteria-derived short-chain fatty acids (SCFA) to *germ free* mice induced an increase of Treg cells number, and reduced allergic response (56, 59–62). The allergy-protective action of Clostridia was also confirmed in the animal model, where a significant protective effect consisting in regulation of innate lymphoid cell function, Foxp3^{+} Tregs, immunoglobulin (Ig)A and intestinal epithelial permeability was demonstrated (63). A "humanized mice model," created with inoculation of microbiota-derived from human feces, resulted in an increase in Treg cells and a reduction of allergic symptoms (64). The functional role of dysbiosis associated with FA was also revealed by the different capacity of the gut microbiota of allergen-sensitized mice to increase Th2 cells number and IgE responses and to promote allergic sensitization (17).

Unfortunately, data characterizing the gut microbiome of patients affected by FA are still preliminary.

Table 1 summarizes main evidence on FA-associated gut microbiome features. Heterogeneity in study design, used to define the gut microbiome, make it difficult to establish a causal relationship between development of FA and specific bacteria. Despite these limitations, at least four relevant observations on FA-associated gut microbiome can be raised:

- Dysbiosis precedes the FA onset;
- Microbial community structure early in life, particularly in the first 6 months of life, is more relevant in FA development;
- No specific bacterial taxa could be consistently associated with FA onset, with a broad range of microbes that could have positive or negative influence on tolerogenic mechanisms;
- Dysbiosis could influence not only the occurrence, but also the disease course of FA. As suggested by different gut microbiota features comparing children who outgrow FA with patients with persistent form of FA (71).

Recent studies underline the importance of the modulation of gut microbiota through different dietary interventions in pediatric patients with FA. CMA children treated with soy and rice based

BOX 2 | Techniques used to investigate the gut microbiota metagenomic and metabolomic features.

Technique	Description	Advantages	Disadvantages
Metagenomics			
Culture	Isolation of bacteria on selective media	Cheap, semi-quantitative	Labor intensive
qPCR	Amplification and quantification of 16S rRNA. Reaction mixture contains a compound that fluoresces when it binds to double-stranded DNA	Fast,quantitative, Phylogenetic identification	PCR bias, unable to identify unknown species
DGGE/TGGE	Gel separation of 16S rRNA amplicons using denaturant/ temperature	Fast, semi-quantitative, bands can be excised for further analysis	No phylogenetic identification, PCR bias
T-RFLP	Fluorescently labeled primers are amplified and then restriction enzymes are used to digest the 16S rRNA amplicon. Digested fragments separated by gel electrophoresis	Fast, cheap, semi-quantitative	No phylogenetic identification, PCR bias, low resolution
Fish	Fluorescently labeled oligonucleotide probes hybridize complementary target 16S rRNA sequences. When hybridization occurs, fluorescence can be enumerated using flow cytometry	Phylogenetic identification, semi-quantitative, no PCR bias	Dependent on probe sequences—unable to identify unknown species
DNA microarrays	Fluorescently labeled oligonucleotide probes hybridize with complementary nucleotide sequences. Fluorescence detected with a laser	Fast, Phylogenetic identification, semi-quantitative	Cross hybridization, PCR bias, species present in low levels can be difficult to detect
Cloned 16S rRNA gene sequencing	Cloning of full-length 16S rRNA amplicon, Sanger sequencing and capillary electrophoresis	Phylogenetic identification, quantitative	PCR bias, laborious, expensive, cloning bias
Direct sequencing of 16S rRNA amplicons	Massive parallel sequencing of partial 16S rRNA amplicons for example, 454 Pyrosequencing® (Roche Diagnostics GMBH Ltd, Mannheim, Germany) (amplicon immobilized on beads, amplified by emulsion PCR, addition of luciferase results in a chemoluminescent signal)	Fast, Phylogenetic identification, quantitative, identification of unknown bacteria	PCR bias, expensive, laborious
Microbiome shotgun sequencing	Massive parallel sequencing of the whole genome (e.g., 454 pyrosequencing® or Illumina®, San Diego, CA, USA)	Phylogenetic identification, quantitative	Expensive, analysis of data is computationally intense
Metabolomics			
Gas Chromatography Mass Spectrometry (GC-MS)	Thermally stable and volatile compounds are separated by GC and the eluting metabolites are detected by electron-impact (EI) mass spectrometers.	High efficiency, reproducibility and sensitivity	It can only be performed for volatile compounds
Liquid Chromatography Mass Spectrometry (LC)	Allows to separate compounds with little effort in a few pre-analytics steps (compared to GC-MS). The metabolite separation obtained with LC is followed by electro spray ionization (ESI) or atmospheric chemical ionization under pressure (APCI)	Lower temperatures of analysis, and it does not require sample volatility. Sensitivity, specificity, resolving power, and capability to extract additional information about metabolites from their retention time (RT) domain.	
Capillary Electrophoresis Mass Spectrometry (CE)	Offers high-analyte resolution and detect a wider spectrum of (polar) compounds compared to HPLC.	High resolution	It is properly applicable only to charged analytes
Fourier Transform Infrared Spectroscopy (FTIR)	Allows rapid, non-destructive and high-throughput determination of different sample types. This technique allows detecting different molecules, such as lipids and fatty acids (FAs), proteins, peptides, carbohydrates, polysaccharides, nucleic acids.	Ultra-high mass resolution able to distinguish slight variations in a wide number of mass signals, and allowing to obtain the structural identification of new biomarkers	Not high sensitivity and selectivity
Nuclear Magnetic Resonance Spectroscopy (NMR)	It uses the intramolecular magnetic field around atoms in molecules to change the resonance frequency, thus allowing access to details of molecules' electronic structure and obtaining information about their dynamics, reaction state, and chemical environment.	Useful to determine metabolic fingerprints leading to the identification and quantification of compounds in a non-targeted large-scale, in a non-destructive way, and with a high reproducibility	It is a relatively insensitive technique, and can only detect metabolites in high concentrations

formula showed low fecal abundance of *Coriobacteriaceae* and *Bifidobacteriaceae*. Contrarily, *Coriobacteriaceae*, and certainly the genus Collinsella, the major bacteria that metabolized lactose in the gut, resulted increased in CMA children that consumed extensively hydrolyzed formula. In the same study, the authors found that fecal butyrate levels are positive correlated with abundance of *Coriobacteriaceae* (77). We showed that the treatment with extensively hydrolysed casein formula (EHCF)

TABLE 1 | Main gut microbiome features in food allergy.

	OTUs	Diversity	Technology	Main features	References
Björkstén et al. (65) (*n* = 62; FA)	N.R.	N.R.	*Bacterial culture*	↑*Coliforms, S. Aureus* ↓*Lactobacilli, Bifidobacteria*	(65)
Thompson-Chagoyan et al. (66) (*n* = 46:FA)	↑	N.R.	*Bacterial culture*	↑ *Lactobacilli* ↓*Bifidobacteria*	(66)
Thompson-Chagoyan et al. (67) (*n* = 46:FA)	N.R.	N.R.	*Bacterial culture*	↑*C.coccoides*, *Atophium cluster*	(67)
Nakayama et al. (68) (*n* = 11: FA)	=	=	16s rRNA sequencing	↑*Bacteroides,Propionibacterium*, *Klebsiella* ↓*Acinobacterium, Clostridium*	(68)
Ling et al. (69) (*n* = 34: FA)	↓	=	16s rRNA sequencing	↑ *Bacteroidetes*, *Proteobacteria*, *Actinobacteria* ↓*Firmicutes*	(69)
Azad et al. (55) (*n* = 12: FS)	↓	=	16s rRNA sequencing	↓*Enterobacteriaceae*, *Bacteroidaceae*	(55)
Chen et al. (70) (*n* = 23: FS)	N.R.	↓	16s rRNA sequencing	↑*Firmicutes*, *Proteobacteria*, *Actinobacteria* ↓*Veillonella*	(70)
Berni Canani et al. (53) (*n* = 39; FA)	↑	N.R.	16s rRNA sequencing	↑*Ruminococcaceae*, *Lachnospiraceae* ↓*Bifidobacteriaceae*, *Streptococcaceae*, *Enterobacteriaceae*	(53)
Bunyavanich et al. (71) (*n* = 226; FA)	↑	N.R.	16s rRNA sequencing	↑*Bacteroidetes*, *Enterobacter*	(71)
Inoue et al. (72) (*n* = 4: FA)	N.R.	N.R.	16s rRNA sequencing	↑*Lachnospira*, *Veillionella*, *Suterella* ↓*Dorea*, *Akkermansia*	(72)
Kourosh et al. (73) (*n* = 68; FA)	↑	N.R.	16s rRNA sequencing	↑*Oscillobacter valericigenes*, *Lachnocrostidium bolteae*, *Faecalibacterium* sp.	(73)
Fazlollahi et al. (74) (*n* = 141; FA)	N.R.	N.R.	16s rRNA sequencing	↑*Lachnospiraceae*, *Streptococcaceae*, *Leuconostocaceae*	(74)
Dong et al. (75) (*n* = 60; FA)	N.R.	↓	16s rRNA sequencing	↑*Lactobacillaceae*, ↓*Bifidobacteriaceae*, *Ruminococcaceae*	(75)
Berni Canani et al. (76) (*n* = 46; FA)	=	=	16s rRNA sequencing	↑*Bacteroides, Alistipes*	(76)
Diaz et al. (77) (*n* = 27; FA)	N.R.	N.R.	16s rRNA sequencing	↑*Coriobacteriaceae*	(77)

FA, food allergy; FS, sensitization to food antigens; OTUs, operational taxonomic units; N.R., not reported; ↑*, increase;* ↓*, decrease.*

containing the probiotic *L. rhamnosus* GG (LGG) in CMA children significantly increased SCFA-producers bacteria and butyrate fecal levels. These effects were associated with immune tolerance acquisition (76).

Targeting Gut Microbiome in FA

The Importance of the Diet-Gut Microbiome Axis

Advances in metagenomics and metabolomics implicate diet and gut microbiome (the diet-gut microbiome axis) as key modulators of the maturation of the immune system. Findings from a recent systematic review further support the relationship between maternal diet during pregnancy and lactation and FA during childhood (78). Diet from conception (maternal diet) up to the first 24 months of age (baby diet), may influence the risk of developing FA (78–81). A recent study suggests that a healthy diet with high levels of fruits, vegetables and home-made foods is associated with less FA at the age of 24 months (82). Several studies have reported that nutrients impact the gut microbiota and the production of bacterial metabolites (83, 84). The Mediterranean diet (MD) is defined as a healthy balanced diet. It is characterized by high consumption of assorted cereals, legumes, fruits, vegetables, olive oil, and nuts; moderate consumption of red wine, poultry and fish, and a lower intake of red meat and sweets. MD during pregnancy and early life has been demonstrated to have a protective role against allergic disease in children (85). These effects could derive from the high intake of non-digestible dietary carbohydrates (NDC), the beneficial fatty acid profile that is rich in omega-3, the high levels of polyphenols, and other antioxidants (86). Non-digestible dietary carbohydrates represent the primary nutrient source for gut bacteria, and their fermentation leads to the production of SCFAs) (53, 87). It has been demonstrated that

reduced availability of NDC lowered the concentration of fiber-degrading bacteria and increased mucin-degrading bacteria (88). High adherence to the MD has been associated with-increased levels of *Prevotella* bacteria and other *Firmicutes* and of SCFAs production (89). The immunomodulatory mechanisms elicited by SCFAs represent one of the strongest connections between diet, gut microbiome and allergic diseases (90). Major SCFAs included acetate, propionate, butyrate, and valerate (87). SCFA-producing bacteria represent a functional group, including *Faecalibacterium prausnitzii* and *Eubacterium rectal*, *Roseburia* are efficient butyrate producers (91). SCFAs are major energy source for colonocytes and influence epigenetically several non-immune (tight junction proteins, mucus production) and immune functions (macrophages, neutrophils, dendritic cells (DCs), T and B cells) involved in the immune tolerance network (92–98). SCFAs interaction with enterocytes are mediated by G-protein coupled receptors, namely GPCRs; GPR41, GPR43, GPR109A, and Olfr78) (99–101). GPR43 and GPR41 are highly expressed by enterocytes (102), whereas immune cells express GPR43 and GPR109A (100, 103–106). Among SCFAs, butyrate exerts a pivotal role in immune tolerance induction. It has been found that SCFAs are able to increase colonic Treg frequency and *in vitro* treatment of colonic Tregs, from germ free mice, with propionate significantly increased *FoxP3* and IL-10 expression, a key cytokine that regulate Treg functions (60). Similarly, it has been demonstrated that butyrate facilitates generation of activated FoxP3^{+} Treg in mouse model (107).

Butyrate is able to regulate 103^{+}DCs, reducing pro-inflammatory cytokines production and enhancing retinoic acid (RA) expression and subsequent generation of RA-regulated tolerogenic DCs (108). Butyrate promotes B cell differentiation and increases IgA and IgG production (107, 109).

The mechanisms are multiple and involve a strong epigenetic regulation of gene expression through the inhibition of histone deacetylase (HDAC) (60, 110, 111).

Butyrate deficiency has been observed in allergic children (112). Bacteria-produced SCFAs have been studies, has been specifically attributed to butyrate production by spore-forming Clostridiales. An enrichment of butyrate-producing taxa (Clostridia class and *Firmicutes phylum*) has been observed in children with faster CMA resolution (71). Altogether, these data suggest the potential of a "post-biotic" approach, based on the use of SCFAs against FA. In this light, data from our laboratory showed that oral butyrate induces a dramatic inhibition of acute allergic skin response, anaphylactic symptom score, body temperature decrease, intestinal permeability increase, anti-β lactoglobulin (BLG) IgE, IL-4, and IL-10 production in a murine model of CMA, suggesting a protective role of butyrate against FA (113).

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 cytokine genes. The same effective butyrate dose induces *FoxP3* demethylation and down-regulation of HDAC6/HDAC9 expression (113, 114).

TABLE 2 | Main preclinical evidences on the probiotics role against food allergy.

Biological effects	Bacterial strains	References
Intestinal barrier maturation	*B. lactis/bifidum*; *L. rhamnosus GG*	(128, 130, 135)
Th1/Th2 response balance: Th1 stimulation	*B. lactis/bifidum/ infantis*; *L. acidophilus/reuteri; L. rhamnosus GG*	(132, 133, 136, 137)
Th1/Th2 response balance: Th2 suppression	*B. bifidum/infantis/longum; L. actobacillus acidophilus/reuteri; L. rhamnosus GG*	(132, 134, 138–140)
Immune system regulation: Tregs development	*B. bifidum/infantis/lactis; L. acidophilus/reuteri/casei; L. rhamnosus GG*	(132, 134, 137)
Increase in B and T cell proliferation with enhanced production of Th1 and regulatory cytokines	*L. acidophilus; L. casei; L. salivarius; L. lactis; B. infantis; B. lactis; B. longum*	(135)
Immune system regulation: tolerogenic DCs development	*B. bifidum; L. reuteri/casei*; *L. rhamnosus GG*	(134, 137, 141, 142)
Suppression of IgE production	*B. bifidum/longum*; *B. lactis Bb-12*; *L. acidophilus*; *L. rhamnosus GG*	(128, 133, 138, 143, 144)
Epigenetic modulation of Th1/Th2 genes expression	*B. breve; L. rhamnosus GG*	(145–147)
Increase in the production of the regulatory cytokine IL-10 by monocytes and dendritic cells; enhance of IFN-γ production by T cells	*L. plantarum; B. adolescentis*	(141, 148, 149)
Increase in the population of CD4^{+}FoxP3^{+} T cells, up-regulation of FoxP3 and down-regulation of GATA-3	*L. plantarum; B. coagulans*	(145)
Reduction of allergic reaction; reduction of IL-4, IL-5, IL-13 and specific IgE production	*L. rhamnosus GG*	(139)
Improvement of anaphylaxis symptoms and increase of sIgA and CD4^{+} CD25^{+} FoxP3Treg cell	*C. butyricum*	(150)

Additional potential mechanisms by which diet could 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 (115). Tryptophan is an essential amino acid, which cannot be synthesized independently by humans; thus, it must be ingested through the diet. A portion of tryptophan is utilized to synthesize protein, and the other portion is catabolized to produce a variety of bioactive compounds, such as kynurenine (Kyn), serotonin and melatonin (84). Tryptophan absorbed by enterocytes directly activates the mTOR pathway by intracellular tryptophan receptors (116, 117). mTOR is known to play an important role in connecting metabolism and the immune system. During an inflammatory process,

tryptophan is metabolized through the Kyn pathway. Kyn is an active metabolite and its biological activity is mediated by aryl hydrocarbon receptor (AhR) (118). The bond of Kyn to AhR receptor lead to the inhibition of DCs maturation and the proliferation of Th17 cells and Treg, increasing IL-22 and IL-10 production (119–122). Indole, indole 3-propionic acid (IPA) and indole-3-aldehyde (I3A) are produced by catabolism of tryptophan through intestinal commensal bacteria. A study demonstrated that strains of *Clostridium cadaveris* and *Peptostreptococcus anaerobius* CC14N metabolize tryptophan to produce IPA. Tryptophan can be also catabolized by lactobacilli to I3A. This metabolite protects gut mucosa against inflammation through AhR recognition (123). Indole-3-carbinole (I3C), an AhR ligand, has been demonstrated to boost immune tolerance in an ovalbumin (OVA)-sensitized mouse model (124). Mice fed I3C showed lower titres of anti-OVA IgG1 antibodies and higher number of CD103$^+$MHC-II$^+$ tolerogenic DCs compared to normal chow-fed control mice (124).

Engineering Gut Microbiome With Probiotics in FA

Immune tolerance is a major therapeutic target in FA. Evidence supports the concept that probiotics, defined as live microorganisms which when ingested in adequate amounts confer a beneficial effect on the host (125), could act at different levels in the immune tolerance network: modulating gut microbiota structure and function (increased production of butyrate) (53); interacting with enterocytes with subsequent modulation of non-immune (gut permeability and mucus thickness) (126–129) and immune tolerogenic mechanisms (stimulation of sIgA and β-defensins production) (130); modulation of cytokine response by immune cells (110–113, 131–134). Main pre-clinical evidence on probiotic activity against

Box 3 | Targeting gut microbiota against FA: a research agenda.

Targets	Possible strategies
Identifying specific gut microbiota features associated with FA	To comparatively analyze metagenomics and metabolomics features of well-characterized populations of patients affected by different types of FA(naive of any dietary treatment) and healthy well-matched controls.
Characterizing the effect of dietary intervention and probiotic therapy	Prospective studies analyzing gut metagenomic and metabolomics changes in well-characterized populations.
Identifying the best probiotic strain to treat FA	Studies on mechanisms action in *in vitro* and in *in vivo* models. Clinical trials with well-characterized probiotic strains and doses involving patients with challenge-proven diagnosis of FA.
Optimizing the post-biotic approach to treat FA	Full characterization of the bio-functional features of gut microbiota metabolites that could be used against FA. Studies on mechanisms action in *in vitro* and in *in vivo* models. Clinical trials with well-characterized products involving patients with challenge-proven diagnosis of FA.

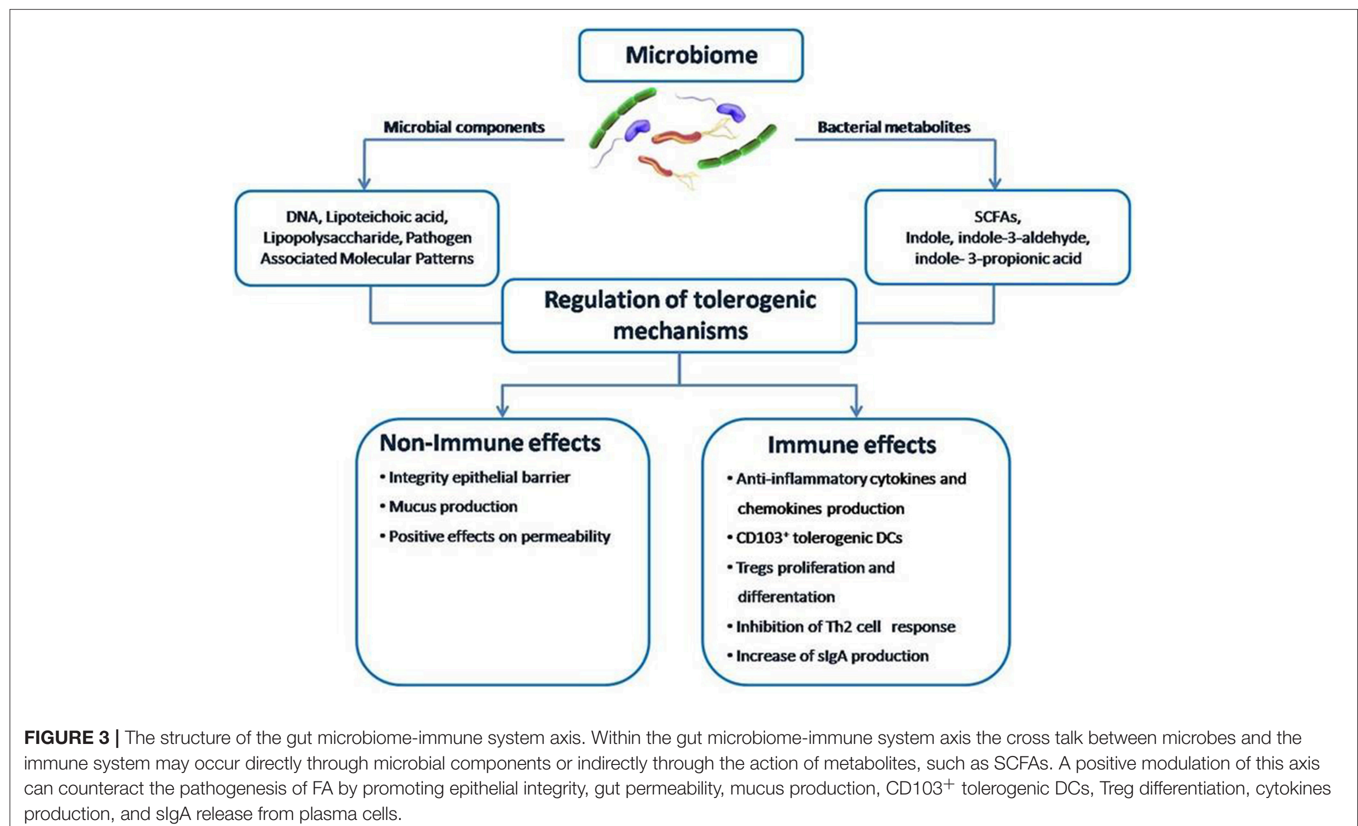

FIGURE 3 | The structure of the gut microbiome-immune system axis. Within the gut microbiome-immune system axis the cross talk between microbes and the immune system may occur directly through microbial components or indirectly through the action of metabolites, such as SCFAs. A positive modulation of this axis can counteract the pathogenesis of FA by promoting epithelial integrity, gut permeability, mucus production, CD103$^+$ tolerogenic DCs, Treg differentiation, cytokines production, and sIgA release from plasma cells.

FA are summarized in **Table 2**. In the last decades, a number of experimental investigations have been developed to characterize organisms that could be used to modulate the immune system of patients with FA. Stimulation of human 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 *L. plantarum* and *B. adolescentis* resulted in an increased production of the regulatory cytokine IL-10 by monocytes and DCs, and to enhanced IFN-γ production by T cells) (138, 148, 149). The addition of a probiotic mixture (*L. casei* W56, *L. lactis* W58, *L. acidophilus* W55, *L. salivarius* W57, *B. infantis* W52, *B. lactis* W18, and *B. longum* W51) to PBMCs from children with FA stimulated an increase of Th1 cells and related cytokines (141). An increase in T and B cells 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 (141). 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 the probiotics *B. breve* and LGG inhibit activation of proinflammatory cytokines, IL-23, and IL-17, thereby reducing histone acetylation and simultaneously enhancing DNA methylation (135). The limitation of studying the effect of probiotics *in vitro* lies in the extrapolation of the results of *in vivo* benefits. For that reason, another commonly used experimental tool in this area is based on the use of animal model of FA. Using an OVA mouse model, it was demonstrated that oral administration of *B. infantis* reduced serum OVA-specific IgE, and IgG1 levels and Th2 cytokine release from splenocytes. Moreover, gut microbiota analysis showed that the probiotic-mediated protection was conferred by high abundance of *Coprococcus* and *Rikenella* (151). Different effects of oral administration of *B. coagulans* 09.712, *L. plantarum* 08.923, and *B. infantis* 11.322 in the reduction of Th2-driven intestinal inflammation and other symptoms associated with food-induced anaphylaxis, were demonstrated in a murine model of shrimp allergy (145). In particular, oral supplementation with *B. coagulans* 09.712 and *L. plantarum* 08.923 significantly ameliorates anaphylaxis symptoms and increases the population of $CD4^{+}$ $CD25^{+}FoxP3^{+}$ T cells through mTORC inhibition, FoxP3 upregulation, and GATA-3 downregulation (145). Oral treatment with *C. butyricum* significantly ameliorated anaphylaxis symptoms and increased sIgA and $FoxP3^{+}$Treg cells in the spleen from BLG-sensitized mice (150). Neonatal monocolonization of germ-free mice by *L. casei* BL2 modulated the allergic sensitization to cow's milk proteins, developed higher IgG responses against caseins, elicited by *L. casei* hydrolysed insoluble caseins into soluble immunogenic peptides (152). Similar results were obtained by others who observed a decrease of concentrations of IgE, IL-4, and IL-13 following administration of *B. infantis* CGMCC313-2 in BLG-sensitized mice (153). Oral administration of VSL#3 (a mixture of *Streptococcus thermophilus* BT01, *B. breve* BB02, *B. longum* BL03, *B. infantis* BI04, *L. acidophilus* BA05, *L. plantarum* BP06, *L. paracasei* BP07, *L. delbrueckii* subsp. *bulgaricus* BD08) to sensitized mice significantly reduces Th2 immune responses and protects against anaphylactic reactions in a mouse model of FA (154). Also, the incubation of mouse spleen cells from sensitized mice with probiotic mixture reduced allergen- stimulated IL-13 and IL-5 production and increased of IFN-γ and IL-10 production (154). An immunoregulatory action by LGG has been demonstrated in a murine model of CMA. LGG administration suppressed Th2 responses, such as reduced hypersensitivity score and lowered serum CMP-specific IgG1, while promoting IFN-γ and CMP-specific IgG2a levels (155). Similar results have been reported by our group in a BLG-sensitized mice model, in which we found that the administration of LGG added to EHCF elicited a significant

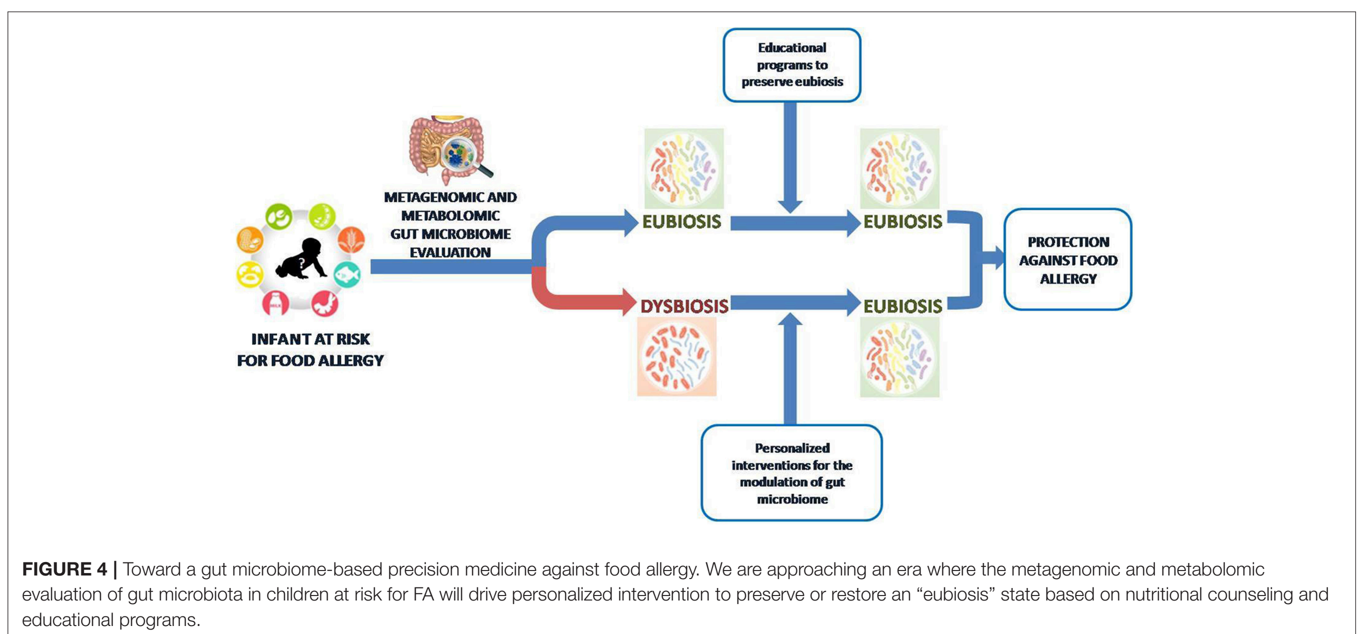

FIGURE 4 | Toward a gut microbiome-based precision medicine against food allergy. We are approaching an era where the metagenomic and metabolomic evaluation of gut microbiota in children at risk for FA will drive personalized intervention to preserve or restore an "eubiosis" state based on nutritional counseling and educational programs.

reduction of allergic reaction, and of IL-4, IL-5, IL-13 and specific IgE production (139).

Clinical studies have investigated the efficacy of selected probiotic strains against FA. The effect appears strain-specific and more evident in the pediatric age group. In a randomized double-blind placebo-controlled trial, it was demonstrated that the administration of *L. casei* CRL431 and *B. lactis* BB12 added to hypoallergenic formula for 12 months did not modulate the rate of immune tolerance acquisition to cow's milk proteins in infants with CMA (140). Using a similar study design, we have demonstrated that EHCF containing the probiotic LGG is able to accelerate immune tolerance acquisition in CMA children. Children (aged 1–12 months), consecutively referred for suspected CMA (IgE- or non-IgE-mediated), but still receiving cow's milk proteins, were evaluated in the study. Subjects were randomly allocated to one of the two groups of dietary interventions: EHCF (control group); and EHCF containing LGG (at least 1.4×10^7 CFU/100 mL; active group). 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%, $p = 0.027$)] (156). The results were confirmed in a subsequent trial, when the effect of 5 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 immune tolerance to cow's milk proteins was significantly higher in the group receiving EHCF+LGG (78.9%) than in other groups (157). 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 (158). 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 (159–162), and by an expansion of butyrate- producing gut microbiota (53, 76). Accordingly, studies in children with eczema and/or CMA who received EHCF plus LGG showed benefits in decreasing inflammation and gastrointestinal symptoms (163). Probiotics have been also proposed to reinforce the effectiveness of immunotherapy (164). 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 leads to tolerance. Randomized double-blind placebo- controlled trial was performed in 62 children with peanut allergy treated with fixed dose of probiotic together with peanut OIT (PPOIT) or placebo once daily for 18 months (165). Sustained unresponsiveness (SU), determined by double blind placebo controlled food challenge (DBPCFC), was achieved in 82.1% of children receiving PPOIT compared with 3.6% of those receiving placebo. PPOIT also induced high rates of resolution (90%) and was associated with reduced skin prick test reactivity, decreased peanut-specific IgE and increased peanut-specific IgG4 levels. No participants withdrawing because of adverse reactions.

No OIT control group was evaluated to determine if the probiotic itself had any effect on SU (165). Further studies are required to evaluate this approach comparing peanut OIT and probiotics with peanut OIT with placebo or probiotic alone.

CONCLUSIONS

Gut microbiome could be a promising target for innovative therapeutic and preventive strategies against FA. The results of the studies are encouraging, but more data are needed to better define the potential of modulating the diet-gut microbiome–immune system axis to fight FA (**Figure 3**). We are approaching a new era in which we can regulate immune system development and function through dietary intervention and measure the clinical impact through gut microbes and their metabolites. Given the current gaps in the investigational approaches and data analysis and interpretation, we need more scientific evidence that can be translated in clinical practice (**Box 3**).

Understanding how nutrients and metabolites, or probiotics could influence gut bacteria communities and the immune system will contribute to building up a precision medicine approach for FA care (**Figure 4**).

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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