Gut Microbiota as a Target for Food Allergy

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ABSTRACT

Purpose of review: The purpose of this review is to present an overview on the potential role of gut microbiota as target of intervention against food allergy.

Recent findings: Many studies suggest a key pathogenetic role for gut microbiota modifications (dysbiosis) in food allergy development. Several factors responsible for dysbiosis have been associated with the occurrence of food allergy, such as caesarean delivery, lack of breast milk, drugs use (mainly antibiotics and gastric acidity inhibitors), antiseptic agents use, and low fibers/hight fat diet. No specific bacterial taxa have been consistently associated with food allergy, but evidence suggests that gut dysbiosis occurs even before food allergy signs and symptoms presentation. Data from animal and human studies highlight the ability of particular bacterial taxa to ferment dietary fibers for the production of short chain fatty acids that affect host immunity and help to explain their health-promoting role.

Summary: Modulation of gut microbiota composition and/or function represents a promising strategy for treatment and prevention of food allergy in childhood.

Key Words: butyrate, dysbiosis, oral tolerance, probiotics, short chain fatty acids

Abbreviations: BLG, beta-lactoglobulin, CMA, cow's milk allergy, EHCF, extensively hydrolyzed casein formula, FA, food allergy, HDAC, histone deacetylase, LGG, Lactobacillus rhamnosus GG, PBMCs, peripheral blood mononuclear cells, SCFAs, short chain fatty acids, TGF-β, transforming growth factor beta, Treg, regulatory T cell

INTRODUCTION

During the last decades, the pattern of food allergy (FA) is changed with increased persistence, severity of clinical manifestations and economic impact (1). Thus, there is a strong need to develop effective strategies to stimulate oral tolerance acquisition and maintenance.

The cause of FA is still largely undefined. Based on current knowledge genetic factors may predispose towards development of FA among selected individuals; but genetic variance alone cannot explain the changing pattern of FA, renewing interest in the role of the environment in shaping sensitization to food. In particular, many studies suggest a key pathogenetic role for gut microbiota alterations (dysbiosis) in FA development.

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The purpose of this review is to present an overview on the potential role of gut microbiota as target of intervention against FA by providing an answer to four key questions.

Question #1: Is There A Link Between Microbial Exposure and Food Allergy?

The complex interaction between gut microbiota and immune and non-immune cells results in an environment that favours oral tolerance (Fig. 1). The maturation of a healthy gut microbiota in early life allows for a change in the Th1/Th2 balance, favoring a Th1 cell response; while dysbiosis alters host-microbiota homeostasis producing a shift of the Th1/Th2 cytokine balance, toward a Th2 response. Colonic microbes induce regulatory T cells (Tregs) activation and these cells are depleted in germ-free mice (2). The microbiota-induced Tregs express the nuclear hormone receptor RORγt and differentiate along a pathway that also leads to Th17 cells; while in the absence of RORγt in the Tregs, there is an expansion of Tregs that express GATA-3 as well as conventional Th2 cells and Th2-associated pathology is exacerbated (3). Thus, microbiota educates Tregs to suppress Th2 response, and in the absence of this education process, Tregs can deviate to a phenotype that not only not suppress FA but contributes to it (4).

Several factors responsible for dysbiosis have been associated with the occurrence of FA, such as caesarean delivery, lack of breast milk, drugs use (mainly antibiotics and gastric acidity inhibitors), antiseptic agents use, and low fibers/hight fat diet (2). Data emerging from human studies link the use of antimicrobial agents to the increasing prevalence of FA. It has been demonstrated that neonatal antibiotic treatment reduced microbial diversity and bacterial load in both faecal and ileal samples and enhanced food allergen sensitization (5). Even low-dose early-life antibiotic exposure can lead to long-lasting effects on metabolic and immune responsiveness (6). Maternal use of antibiotics before and during pregnancy, as well as antibiotic courses during first months of life, are associated with an increased risk of cow's milk allergy (CMA) in infants (7).

A recent study examining the influence of dietary patterns on the development of FA at the age of two years suggests that the dietary habits may influence the development of FA by changing the composition of the gut microbiota. In particular, an infant diet consisting of high levels of fruits, vegetables, and home-prepared foods was associated with less FA (8).

Question #2: Is There A Particular Signature in Food Allergy-Related Dysbiosis?

Although compelling evidence for gut microbiota dysbiosis association with FA is emerging, some studies have failed to find differences in infant microbiota according to later allergic status or have found different changes in gut microbiota. Heterogeneity in study design, including sampling time points, methods used to characterize microbiota, and different allergic phenotypes under study, make it difficult to establish a causal relation between specific bacterial taxa and development of allergy (2). No specific bacterial taxa have been consistently associated with FA and a broad range of microbes isolated from human gut could be involved in tolerogenic mechanisms. In FA children compare to healthy subjects, different levels of SCFAs, in particular of butyrate, have been described (9–11). Thus, 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 FA.

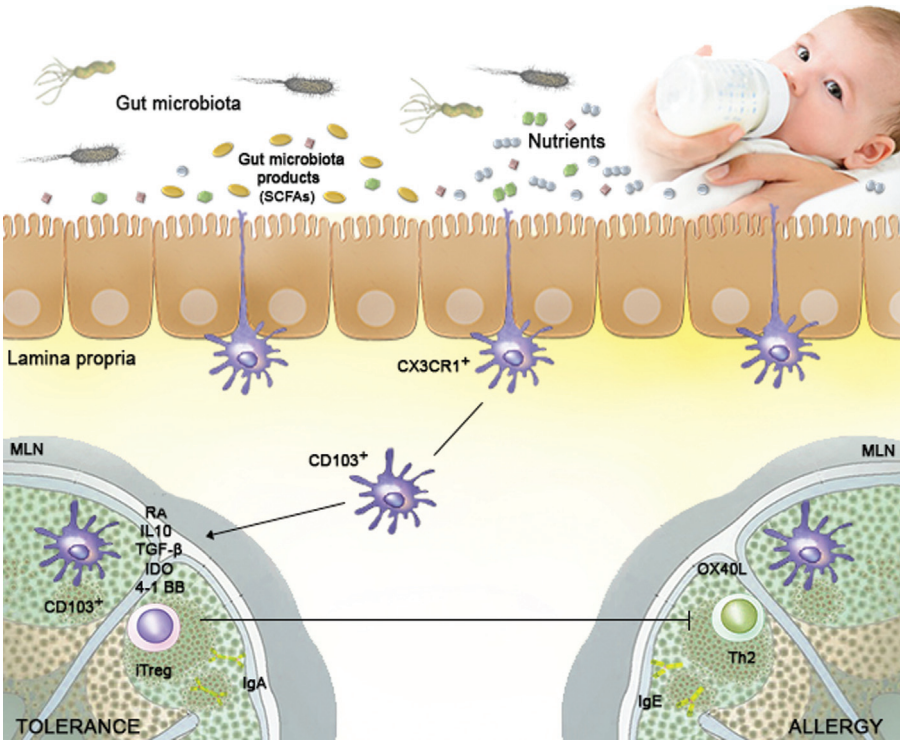

FIGURE 1. The oral tolerance network. The oral tolerance network is mainly composed by the well-modulated activity of different components: gut microbiota (without gut microbiota it is not possible to achieve oral tolerance); food antigens; epithelial cells; dendritic cells; regulatory T cells. Food antigens and intestinal microbiota constitute the majority of the antigen load in the intestine. A subset of dendritic cells (DCs) mediates the selective induction of regulatory T cells (Tregs) in response to food antigens encountered in the gastrointestinal mucosa. CD103+ DCs are migratory and traffic to the mesenteric lymph nodes (MNL). CD103+ CDs in the MNL express high levels of transforming growth factor (TGF)-β and the retinoic acid-synthesizing enzyme (RALDH), which facilitate the production of retinoic acid (RA) from vitamin A. CD103+ CDs in the MNL also express the enzyme IDO. TGF-β, RA and IDO are factors that actively promote the development of Tregs from naïve T cells in the MNL. In a broader view, the complex interaction between intestinal contents and immune and non-immune cells result in an environment that favours the tolerance by the induction of IgA antibodies and Tregs, which produce IL-10, dispensable for the induction of tolerance to food antigens.

Question #3: Food Allergy and Changes in Gut Microbiota Composition: What Comes First?

Recent evidence supports the concept that gut dysbiosis during early life can influence the subsequent development of allergic disease (12). In the field of FA, new data suggest that gut dysbiosis precedes FA. Nakayama et al. profiled the faecal bacteria compositions in allergic and non-allergic infants and correlated some changes in gut microbiota composition with allergy development in later years (13).

Azad et al. found that an increased Enterobacteriaceae/Bacteroidaceae ratio and low Ruminococcaceae abundance, in the context of low gut microbiota richness in early infancy, are associated with subsequent food sensitization, suggesting that early gut dysbiosis contributes to subsequent development of FA (14).

Question #4: Which are the Good Bugs?

Data from Animal Studies

Regulatory T cells, which express the Foxp3 transcription factor (Foxp3+Tregs), play a critical role in oral tolerance. The pivotal study from Atarashi et al. showed that the spore-forming component of gut microbiota, particularly clusters IV and XIVa of the genus Clostridium, promoted Tregs accumulation in the colonic mucosa. Colonization of mice by a defined mix of Clostridium strains provided an environment rich in transforming growth factor β (TGF-β) and affected colonic Foxp3+ Tregs number and function (15). In a subsequent study, Atarashi et al. (16) isolated 17 strains within Clostridia clusters XIVa, IV and XVIII from a human faecal sample and demonstrated that these strains affect Tregs differentiation, accumulation and function in the mouse colon. Oral inoculation of Clostridium during the early life of conventionally reared mice resulted in resistance to colitis and systemic immunoglobulin E responses in adult mice, suggesting a new therapeutic approach to FA. 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 colonic Tregs (17), which, in some studies, has been specifically attributed to butyrate production by spore-forming Clostridiales (18). Preliminary 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, anti-βLG lactoglobulin (BLG) IgE, IL-4 and IL-10 production in a murine model of CMA, suggesting a protective role of butyrate against FA.

Data from Human Studies

This evidence derived from animal models suggests that therapeutic modulation of the commensal microbiota may be beneficial for the prevention and treatment of FA. Studies

examining the efficacy of currently available probiotics in treating FA have yielded conflicting results. Probiotics were found to lower the risk of eczema when used by women during the last trimester of pregnancy, by breastfeeding mothers or when given to infants. Evidence did not support an effect on asthma, FA, or allergic rhinitis (19). Recently published guidelines for atopic diseases prevention from the World Allergy Organization concluded that there is a likely net benefit in using probiotics in the prevention of eczema in high risk children with a family history of allergic disease (20). Studies investigating the therapeutic effect of probiotics on challenge-confirmed food-allergic infants are scant. In one randomized, double-blind, placebo-controlled study of infants with challenge-proven CMA, administration of Lactobacillus casei CRL431 and *Bifidobacterium lactis* Bb12 for 12 months did not affect the acquisition of tolerance to cow's milk (21). In contrast, we demonstrated in two prospective clinical trials (22,23) that an extensively hydrolyzed casein formula (EHCF) containing *Lactobacillus rhamnosus* GG (LGG) accelerated the development of tolerance acquisition in infants with CMA. When we compared the fecal microbiota of infants receiving this tolerance-inducing probiotic-supplemented therapy to that obtained from infants receiving an EHCF alone, we found statistically significant positive correlations between the abundance of genera with the potential for producing butyrate and the concentration of fecal butyrate in the infants that received EHCF supplemented with LGG (11). Strain-level demarcations for butyrate producing genera (including Roseburia, Coprococcus, and Blautia) identified in infants that acquired tolerance to cow's milk suggest that LGG treatment contributes to acquisition of tolerance by altering the strain-level community structure of taxa with the potential to produce butyrate (11). The mechanisms of action of butyrate are multiple, but 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 (24). Our study group 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 down-regulation.

CONCLUSIONS

The trillions of bacteria that populate our gut critically regulate key physiological preventive functions against FA. Environmentally induced changes in the gut microbiota composition and function (butyrate production) create dysbiosis that is linked to an increased risk of FA occurrence. Understanding how gut bacteria communities interact with the immune system are opening the way to novel preventive and treatment strategies for FA.

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