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Chapter

Probiotic Bacteria in Microbiome against Allergy

Najaf Allahyari Fard, Zakie Mazhary and Nahid Javanshir

Abstract

According to the World Allergy Organization (WAO), approximately 20% of the global population suffers from allergies. As per ongoing investigations, their pervasiveness is expanding comprehensively. Allergic diseases are significant because of the high prevalence and constant increase in their costs and adverse effects on human life. Probiotics are proposed as an intervention for the prevention and treatment of allergic diseases. Various mechanisms are considered for the anti-allergic effects of probiotic properties, like detecting related molecular patterns, including DNA motifs or lipopolysaccharides (LPS) of the bacteria, through interaction with host immune systems by Toll-like receptors. In this chapter, the microbiome, allergy, and the role of immunomodulatory probiotics against allergy are discussed.

Keywords: probiotic, microbiome, allergy

1. Introduction

In industrialized countries, more than 20% of the population has symptoms of allergies. The commonness of childhood asthma increased by 50% in the USA from 1980 to 2000. The allergy mechanism is an immune response to the allergen, which is often mediated by the immunoglobulin E (IgE) antibody [1]. Allergies can be a serious risk for individuals. Allergens or pollens represent a small fraction of the proteins that humans are regularly exposed to. The importance of the topic in the uncertainty is the cause of the B and T cells' responses to these proteins [2, 3]. Notably, some proteins that are structurally similar pollens may lead to immune response, known as cross-reactivity [4].

The human body microbiome has a diverse composition of bacteria, archaea, fungi, protozoa, and viruses, which are inhabited mainly in the different epidermal surfaces of the body—the skin and mucosal surface. Some of the species of these microbiotas are identified based on cultural techniques, but due to limitations of these techniques [5], it is suggested that the number of human microbiota exceeds 1000 species or 10 times the number of cells in the entire body with 30 times larger total genome than the human genome.

A majority of these microbiotas are in the gastrointestinal tract, the major source of microbial exposure, and live in symbiosis with their host cells [6, 7]. Given up genes necessary for the survival of the commensal microbiota in other microenvironments and retained genes beneficial for the host with no or little benefit to themselves [8] are the evidences of the symbiotic coevolution of the microbiota and human [9].

The interplay of the immune system with gut microbiota starts from the day of birth and even before that. Early exposure during plasticity and prenatal period

seems to be beneficial to prevent the T helper cell type-2 (Th2)-mediated allergic disease [10]. Th2 phenotype is the dominant one in newborns [11] to prevent rejection in utero. Skewing to Th2 in the immune system leads to the stimulated secretion of IgE by B cells and hence to allergies as seen in germ-free mice with the same condition that results in greater IgE responses to food antigens and failure in producing the proper amount of regulatory T cell (Treg) responses [12–14]. On the other hand, upsurge in the amount of T helper cell type-1 (Th1) also mediates the autoimmune disease [12, 15–19].

Restoring Th1/Th2 is the significant role of the microbiota [20]. The association of microbiota and the immune system is mutual. This engagement results in different signaling pathways through the immune system's molecules that increase immune responses [21]. These regulations are crucial for maintaining the homeostasis of the host and for the prevention of different diseases by inducing secretion of IgA and regulatory T cell (Treg) and stimulation of tolerance in face of common antigens [22]. So the formation, maintenance, and heterogeneity of microbiota are necessary during early life owing to their regulatory and tolerance properties in the immune system [23, 24], as it was confirmed that the lack of microflora during a short time in early life results in defection in immune regulation [15]. The mechanisms of oral tolerance which are necessary to suppress excessive immune reactions to antigens are mediated by Foxp3þ Treg [25] and IgA, which is known as the most abundant immunoglobulin and is vital in establishing the composition of microbiota [26] and strengthening the mucosal barrier function [27].

Although, it is observed that abnormal IgA responses lead to allergy development [28]. So the obligation of equilibrium of the allergy mediators is more sensible now.

Lack of genetic elements such as Toll-like receptors that cause enterocyte proliferation like TLR4 and CD14, which enhance the detection of bacterial LPS by TLR4, and TLR9, which identify the genetic molecules of the microorganisms, also increase susceptibility to allergies [29, 30].

As the priority of the microbiome is proven, some factors are mentioned as follows, to support their presence and diversity in the body. Mode of birth; surgical or natural delivery, the process of contacting microflora in the first moment of the presence. Breast or formula feeding; the extension of contact with microflora. Nutritional patterns; the habit of food, based on people's patterns to eat fatty and fast foods or healthy ones like prebiotics which are considered beneficial for even the microbiota of the host. Antibiotics; the matter of using antibiotics at an early age or the trouble of overuse of them in all ages which impair normal flora. Locality; living in urban areas with all of the stresses, less interaction with nature in contrast with living in rural areas results in losing ancient commensal microbiota. Environmental factors; contacting people or animals. Hygiene; the obsession behaviors or normal ones. Lifestyle; the matter of activity or sedentariness in someone's lifestyle.

Natural delivery and breastfeeding are the first two initial and essential exposures when the immune system is not still mature and needs antigens to active oral tolerance [18, 25, 31]. Contravention of these simple factors grounds reformed patterns of early settlement which may result in the incidence of allergy [32]. Food sensitization especially milk allergy and atopic eczema are examples of reduced gut microbial diversity [33–37].

2. The function of the intestinal microbiota

The microbiome is considered as an active organ because of manufacturing intrinsic signals for shifting postnatal development, inspiration of tolerance

mechanisms and immunogenicity reduction, and resistance against invasive pathogens [38–42].

Consuming substrates of the microbiota containing fibers and mucins provides additional energy for the host as fatty acids [43]. Amines, sulfides, and ammonia are the products of them, which are detrimental metabolites for the human.

The protective barrier function against the invasive microbes by their colonization in the intestine is another potential of the microbiota. Different mechanisms for the resistance colonization of the microbiota are considered, such as competition for nutrients and connection to the binding sites and secretion of the antimicrobial substances [44].

Stimulation of the innate signaling pathways through the straight cell-to-cell communications or secretion of short-chain fatty acids (SCFA) are the other regulatory actions of the microbiota. SCFAs produced by the microbiota can direct intestinal Treg cells and inhibit pro-inflammatory responses [45–48].

3. The intestinal microbiota of allergic ones

The role of maternal microbiota in the process of preventing allergy has been proven. Infants from allergic parents are at least twice more likely to the risk of developing allergic diseases than nonallergic parents. Microbiota diversity exists between allergic and nonallergic persons. Reduction in the fecal diversity of the bacteroidetes in pregnancy is connected with the prevalence of atopic eczema in their young children [49]. The microbiota of healthy infants with nonallergic parents frequently consists of healthy lactobacilli, representing the role of maternal microbiota in preventing allergic disorders. A decrease in the number of lactobacilli and bifidobacteria and an increase in the colonization of *Staphylococcus aureus* and *Clostridium difficile* are associated with the development of allergic disorders later in life, which shows the abnormality even before the onset of the allergy [50, 51]. Apart from quantitative alterations, qualitative alterations are important in the microbiota. For example, the microbiota of infants suffering from atopic dermatitis (AD) consists of mostly *B. adolescentis* which is mainly forming adult microbiota, whereas *B. bifidum* is the fundamental former of the healthy breastfeeding infants [52, 53]. Bifidobacteria of atopic dermatitis infants encourage the secretion of pro-inflammatory cytokines, whereas the bifidobacterium of healthy ones encourages the secretion of anti-inflammatory cytokines [54]. Besides, these bifidobacteria have different adhesion behaviors to Caco-2 tissue culture cells [55] and intestinal mucus [56], which seems to be the reason for the reduction in stimulating the immune system. And at last, the metabolic activity of the microbiota composition is different too. Higher levels of butyrate, isovalerate, and caproate in the fecal matter of children with high risk for developing allergy in comparison with normal children are the confirmation of this claim [57].

4. Stabilizing intestinal bacterial flora

The intestine, the largest immune organ of the body, which is the source of the most antibody-producing cells [58] is the target of triggering maturation of the immune system or the restoration of the impaired commensal bacteria. Stimulation of the immune system is one of the most impressive functions of the resident microbiota of the intestine. Probiotic bacteria are considered as a safe solution for modulation of diminished commensal composition and also as influencer of the immune system in preventing allergic disorders [59]. Lactic acid bacteria and

bifidobacteria are good candidates as probiotics with an appropriate life span, no toxic or pathogenic properties, and no inflammatory induction. The selection of the bacteria as probiotics is mainly based on no harmful side effects during the history of their use for a long time. Consumption of these probiotics aid in balancing the ratio of the intestinal flora, avoiding the inhabiting of the pathogens by preventing the binding of them to the host cells, and suppressing the inflammation, which all are as the result of immune system regulation [60]. The effects of probiotics vary with the dose, strain, and duration of consumption and timing.

But the problem of the probiotics is their longevity and residence in the body of the host, as it was seen that they only remain during the administration period and not after that, showing the transient colonization of the probiotics [61–65].

Long-term effects of probiotics in different periods of everyone's life need to be more investigated in complementary studies.

As it was mentioned, immune tolerance is one of the necessary immune reactions to stop excessive inflammatory reactions. Preservation of this tolerance involves the integrity of the epithelial barrier that is heightened by commensal anaerobes, such as *Clostridium* spp. [15, 16, 66, 67], *Bacteroides fragilis* [68], and *Clostridium* spp. [66, 67], which are potent inducers, persuading Foxp3þ Treg differentiation to maintain mucosal tolerance and intestine integrity. Clostridia class also has adaptation properties in the intestinal cells to the routine exposure of an extended range of the antigens. This adaptation is acquired by the effect of IL-22 secreted by innate lymphoid cells which control enterocyte proliferation, activating the secretion of the mucus and antimicrobial production [16, 69].

5. Probiotics' mechanisms of action in allergic disorders

Immune homeostasis develops in the gut as a relationship between the intestinal microbiota, the luminal antigens, and the epithelial barrier is established. Microbial intestinal colonization starts after conception. This happens when the newborn's sterile gut is slowly colonized by environmental bacteria and by interaction with the mother's intestinal flora and surroundings and probably by genetic factors [70–72]. Exposure to microbial flora early in life causes a transition in the T helper cell type-1 (Th1)/Th2 cytokine balance, promoting a Th1 cell response [73].

An infant's immune system at birth is not completely formed and appears to be geared toward a Th2 phenotype to prevent in utero rejection [74]. Nevertheless, the Th2 phenotype results in a stimulated production of IgE by B cells and therefore raises the risk of allergic reactions by mast cells activation [75, 76]. Early in life microbial stimulation will reverse the Th2 bias and promote the expansion of the Th1 phenotype and promote Th3 cell activity [76]. In this way, their combined activity will lead to B-cells releasing IgA. IgA contributes to the elimination of allergens and hence would reduce the immune system's response to antigens. Th1 phenotype-produced cytokines will also reduce inflammation and promote tolerance toward specific antigens [77].

The hygiene concept states that inadequate or aberrant exposure to environmental microbes is one of the triggers of allergy production and related diseases [78]. As mentioned before, allergic diseases are associated with a change in the Th1/Th2 cytokine balance leading to Th2 cytokine activation and interleukin-4 (IL-4), IL-5, and IL-13 activation as well as IgE production [79, 80]. Probiotics significantly alter the gut microenvironment by encouraging a shift in local microflora and cytokine secretion [81] and can potentially modulate enterocyte Toll-like receptors and proteoglycan recognition proteins, resulting in dendritic cell (DC) activation and a Th1 response. The resulting stimulation of Th1 cytokines can suppress reactions to Th2 [82].

6. Probiotics in atopic dermatitis

Atopic dermatitis (AD) is a widespread chronic inflammatory skin condition with a prevalence of around 20% in children and 2–5% in adults worldwide [83]. In recent years, the function of the intestinal microbiota in the aetiopathogenesis of AD has become increasingly important. Atopic dermatitis probiotic therapy is widely studied, with contradictory outcomes [84]. Probiotics containing *Lactobacillus* spp. for the treatment of infantile atopic dermatitis showed beneficial effects in children. Caution should however be raised when treating children under the age of 1 years of age [85]. In addition, mild subjects are exceptions to that beneficial effect. More studies could be informative in investigating the efficacy of *Bifidobacterium* strains. Further larger studies in the treatment of pediatric AD are also required to examine the health, dose-response profile, and long-term impact of probiotics [86].

7. Probiotics in asthma

Asthma, a chronic complex airway disease, is characterized by reversible airflow obstruction, bronchial hyper responsiveness, and underlying inflammation [87]. In recent decades, the prevalence of asthma has risen. One possible mechanism behind this high prevalence is the microbial hypothesis, which suggests that less microbial exposure upregulates T helper cell type-2 (Th2) cytokine development, leading to a rise in allergic diseases [75]. A meta-analysis found that while perinatal and early-life probiotic administration reduces children's risk of atopic sensitization and total rates of immunoglobulin E (IgE), it may not reduce their risk of asthma [88]. However, in addition to routine treatment, several studies have documented the advantage of using probiotics for treating children with asthma. A randomized, placebo-controlled trial for 7-week treatment with *Enterococcus faecalis* showed reduced peak flow variability in children with asthma [89]. Lee et al. have reported substantial improvements in the pulmonary function of children with asthma following a regimen of supplementation of vegetables, fish oil, and fruit along with probiotic administration. Studies, however, have shown that *Lactobacillus* is safe for children with asthma [90, 91].

8. Probiotics in allergic rhinitis

On these bases, probiotic bacteria are capable of altering immune responses through a range of mechanisms that could minimize allergic reactions to airborne allergens without the side effects of any current drugs, and these possible mechanisms, as shown in **Figure 1**, include regulatory T cells that dampen immune responses and suppress the production of IgE antibodies [92, 93]. There are contradictory studies about the effectiveness of probiotics in treating allergic rhinitis [94]. It is reported that *L. casei* decreased the number of episodes of rhinitis in 64 preschoolers with allergic rhinitis [95]. Nonetheless, another study found that patients treated with *Lactobacillus* GG during the birch pollen season who were allergic to birch pollen and apple food found no improvement in symptom score and no reduced sensitivity to birch pollen and apple following probiotic supplementation [96]. Probiotic consumption increased life performance in allergic rhinitis patients. Blood or immunological parameters did not alter significantly in the probiotic community. This indicates probiotics may be useful in allergic rhinitis, but the data present are not sufficient to make any guidelines for treatment [97, 98].

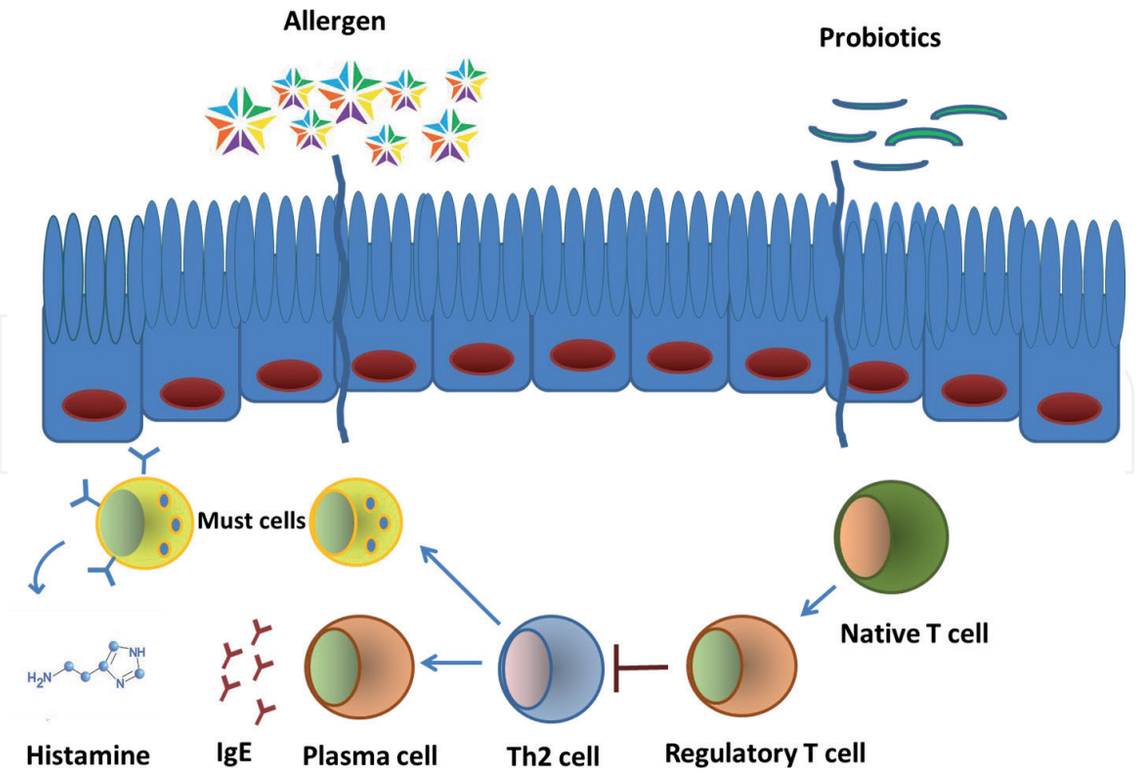


Figure 1.
Probiotic mechanism against the allergen include increasing regulatory T cells that damp down immune responses and suppress the production of IgE.

9. Probiotics in food allergy

Food allergy (FA) is one of the pediatric age's most common allergic disorders and has been considered a global health issue, particularly in the developed world.

Naturally, many subjects with FA outgrow this over time. Cow's milk allergy (CMA), hen's egg allergy, and wheat allergy resolve by 5–10 years in 50% of children. Many FAs (including peanuts, tree nuts, and fish) have low-resolution levels and are seen as persistent [99]. Furthermore, certain types of FA may be correlated with the subsequent development of other allergic symptoms such as oculorhinitis, atopic dermatitis, asthma, and urticaria (the so-called "Atopic March") [100] as well as other diseases such as functional gastrointestinal disorders (FGIDs), inflammatory intestinal diseases (IBD) [101], and psychiatric disorders such as attentive autistic spectrum disorders (ASD).

The gut microbiome-immune system axis that influences the frequency of FA may be modulated by several genetic, environmental, and dietary factors [102]. For example, increased family size, pet and/or rural exposure, balanced diet (full of fibers, fermented foods, antioxidants, omega-3), breastfeeding, and probiotic use are correlated with FA safety. Conversely, C-section, prenatal, and early-life exposure to antibiotics/gastric acid inhibitors/antiseptic agents, unhealthy diet (low fibers/high saturated fats, and junk foods) may increase the risk of developing FA. All these environmental factors mainly operate on a modulation of the structure and function of the gut microbiota, which may in effect be responsible for the epigenetic control of genes involved in immune tolerance.

The pathogenesis of these incidents also is largely unknown, but increasing evidence suggests the hypothesis that disturbance of intestinal microbiome, leading to alterations in the immune system and gut-brain axis, may affect the occurrence of FA and FA-related conditions later in life [103] (**Figure 2**).

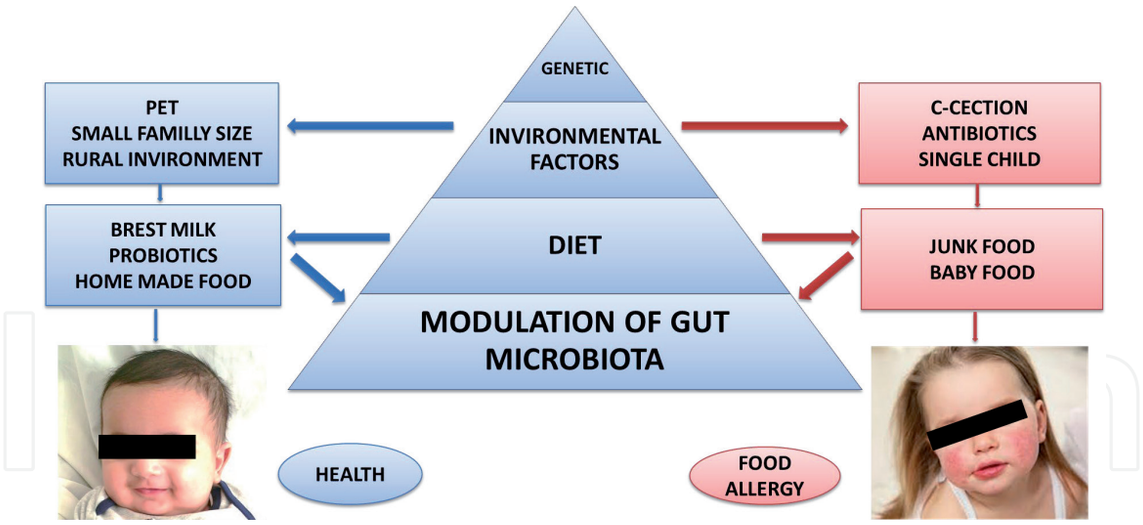


Figure 2.
Good microbiome as a target for food allergy intervention.

Mediterranean diet (MD) is described as a healthy, balanced diet. It is associated with a high intake of assorted cereals, legumes, fruit, vegetables, olive oil, and nuts; moderate consumption of red wine, poultry, and fish; and a lower intake of red meat and sweets. MD has been shown to have a protective role against allergic illnesses in children during pregnancy and early life [104].

Elevated adherence to MD was associated with increased levels of Prevotella and other Firmicutes and production of short-chain fatty acids (SCFAs) [102]. One of the strongest links between diet, gut microbiome, and allergic diseases is the immunomodulatory mechanisms elicited by SCFAs [105]. Common SCFAs contain acetate, butyrate, propionate, and valerate. SCFA-producing bacteria include *Faecalibacterium prausnitzii* and *Eubacterium rectale*. Roseburia is an important butyrate producer [106]. SCFAs are a major source of energy for colonocytes and epigenetically influence many nonimmune functions (tightened junction proteins, and mucus production) and immune functions (macrophages, neutrophils, dendritic cells (DCs), and T and B cells) [107, 108]. Enterocyte interaction of SCFAs is mediated by G-protein-coupled receptors, namely GPCRs, GPR41, GPR43, GPR109A, and Olfr78 [109, 110]. The hopeful target of novel therapeutic and preventive approaches against FA may be the gut microbiome. The results of the studies are promising, but more research is needed for the better definition of the potential for diet-gut microbiome—immune system axis modulation to counter FA. We are entering a new age in which the production and function of the immune system can be controlled by dietary intervention, and the clinical effect can be assessed by gut microbes and their metabolites. Given the current gaps in research methods and data analysis and interpretation, more scientific evidence is required which can be converted into clinical evidence praxis [103].

10. Conclusion

The results of many studies have demonstrated that there is a strong relationship between modifications within the microbiome and many diseases. Much evidence proves that healthy microbiota affects and improves the immune system. It seems that probiotics can have an important role in the prevention of many diseases such as allergy. Microbiota diversity exists between allergic and nonallergic persons. Different mechanisms are considered for the anti-allergic impact of probiotics, like detecting related molecular patterns, including DNA motifs or LPS of the bacteria

by Toll-like receptors. Probiotic mechanism against the allergen includes increasing regulatory T cells that damp down immune responses and suppress the production of IgE.

Acknowledgements

The authors are thankful to the National Institute of Genetic Engineering and Biotechnology (NIGEB), Iran, for providing the facilities.

Conflict of interest

The authors declare no conflict of interest.

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