

Effects of Probiotics on the Immune System and Allergic Diseases

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ABSTRACT

Intestinal microbiota play a crucial role in the development of mucosal tolerance and adaptation. Perturbations in microbiota composition are strongly associated with allergies and asthma in westernized countries. There has been accumulating evidence that the administration of probiotics, "live microbial supplements that exert a beneficial effect on human health," may be effective in the treatment and/or prevention of allergic diseases. Although it has been shown that part of the effect of probiotics arises from its interaction with the host immune system, the precise mechanisms remain to be determined. In addition, future studies are necessary to define appropriate species and strains, optimum dose, frequency, and duration for the treatment of allergic diseases.

KEY WORDS

adaptive immunity, allergic diseases, commensals, epithelial cells, innate immunity, intestinal microbiota, probiotics

INTRODUCTION

Intestinal microbiota, which live in symbiosis with the human body and are major bacterial stimuli received by neonates after birth, are reported to significantly affect human conditions and to be essential for the development and maintenance of the immune system.^{1,2} Recent studies have shown a relationship between intestinal microbiota and the pathogenesis of immunological disorders including allergic diseases.³

These observations suggest that a normalization of intestinal microbiota may lead to an improvement in allergic diseases. Probiotics are defined as "live microbial supplements that exert a beneficial effect on human health," and have been shown to be effective in the treatment and/or prevention of allergic diseases.⁴ Some of these effects are mediated by the interaction of probiotics and the immune system. In this review we focus mainly on interactions of probiotics with innate immunity and their potential for treating allergic diseases.

HUMAN INTESTINAL MICROBIOTA

In the lower intestine of adult humans, the density of commensal bacteria in the lumen reaches 10^{12} organisms per gram of intestinal content, with approximately 400–1,000 species present. The total weight of

microbiota is estimated to be 1 kg. The majority of the bacterial species are strict anaerobes (97%), whereas only 3% are aerobic (facultative anaerobes). The most common anaerobic genera in terms of concentration within the gastrointestinal tract are *Bacteroides*, *Bifidobacterium*, *Eubacterium*, *Fusobacterium*, *Clostridium* and *Lactobacillus*. Among the aerobes are the Gram-negative enteric bacteria (*Escherichia coli* and *Salmonella spp.*) and the Gram-positive cocci (*Enterococcus*, *Staphylococcus* and *Streptococcus*). In addition to aerobic bacteria, aerobic fungal species, such as *Candida albicans*, are also among the normal microbiota. It should be noted that the composition of intestinal microbiota changes in accordance with age (Fig. 1).

ALTERED MICROBIOTA AND DISTURBED IMMUNITY

It has been shown that alterations in the intestinal microbiota can influence mucosal immunity and lead to the development of allergy. Oyama *et al.* showed that the administration of kanamycin to neonatal, but not adult, mice increased the serum levels of total IgG1 and IgE while decreasing the serum IgG2a levels.⁵ The oral introduction of intestinal bacteria into these antibiotic-treated mice prevented the upregulation of basal Th2 responses in the spleen, indicating that the

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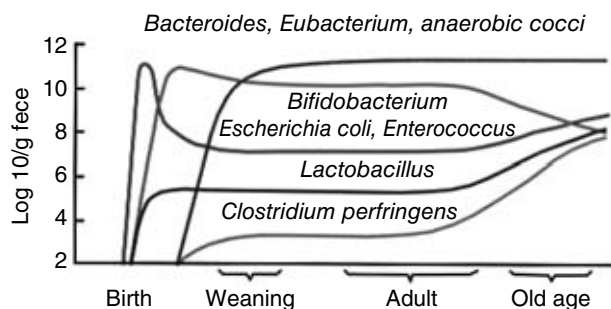


Fig. 1 Chronological changes in intestinal flora (Mitsuoka T. 1972).

mechanism involves the perturbation of intestinal microbiota.⁶ These results suggest that use of antibiotics during infancy may disturb the intestinal microflora and inhibit postnatal Th1-type immune maturation, thus resulting in a Th2-polarized immune deviation and the development of allergic diseases. Several early epidemiological studies have identified a correlation between early antibiotic use in children and the subsequent development of allergies and/or asthma. Among anthroposophic children, the use of antibiotics early in life is significantly associated with the development of asthma.⁷ In addition, it was found that the microbiota of anthroposophic children contain higher levels of lactic acid bacteria than the microbiota of children who had previously been exposed to antibiotics.⁸ However, recent studies do not support the hypothesis that the use of antibiotics in early life is associated with the subsequent development of asthma in childhood, but rather suggest that frequent antibiotic use in early life is more common among asthmatic children.^{9,10} Thus, it is not yet determined that the use of antibiotics in infancy leads to the development of allergic diseases. Nevertheless, accumulating data indicate that altered intestinal microbiota may influence the development of the Th2 response and allergic diseases.

MICROBIOTA IN CHILDREN WITH ALLERGIC DISEASES

Several studies, mostly from northern European countries, indicate that the composition of the intestinal microbiota is different in atopic versus non-atopic individuals.¹¹⁻¹⁵ Bjorksten *et al.* reported that allergic children (as determined by positive skin-prick tests to common allergens) in Sweden and Estonia harbor increased levels of aerobic microbes and decreased levels of anaerobic microbes, particularly *Lactobacillus*.¹¹ Isolauri *et al.* have also reported decreased levels of *Bifidobacterium* and a reduction in the number of Gram-positive organisms among the aerobic populations in infants with atopic eczema.¹² Furthermore, prospective cohort studies suggest that aberrance in intestinal microbiota precedes the development of allergic diseases.^{13,14} Allergic infants have a lower

prevalence of *Bifidobacterium* and a reduced ratio of *Bifidobacterium* to *Clostridium* before the development of allergic manifestations or positive results of skin prick testing.¹³ In another study, infants who developed allergies were found to harbor lower levels of *Bifidobacterium* and *Enterococcus* but increased levels of *Clostridium* and *Staphylococcus aureus* (Table 1).¹⁴

So far, few studies on intestinal microbiota and the development of allergic diseases in infancy have been reported from areas other than northern Europe. Since intestinal microbiota are significantly influenced by genetic and dietary differences,^{16,17} we performed a prospective cohort study on intestinal microbiota in a small population in Japan in which infants born in a hospital were followed from birth to 2 years of age. Our data indicate no aberrant composition of intestinal microbiota at 6 months of age when some infants developed atopic dermatitis or showed positive skin tests. However, allergic infants had higher counts of *Bacteroides*, a higher prevalence of yeast-like organisms, and a higher ratio of *Bacteroides* to *Bifidobacterium* at 2 years of age (Fig. 2). This study suggests that aberrance in intestinal microbiota does not necessarily precede the development of allergy in early infancy, but may become evident after weaning. We speculate that abnormalities in intestinal microbiota are not only the cause for the development of allergic disease, but also a consequence of the intestinal environment resulting from allergic inflammation (Suzuki S *et al.* submitted).

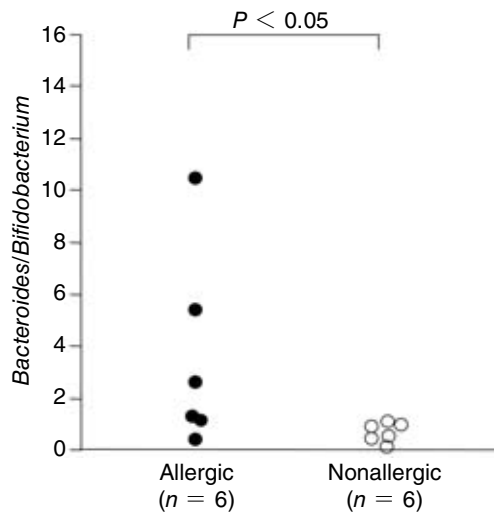
CLINICAL EFFECTS OF PROBIOTICS ON ALLERGIC DISEASES

As mentioned above, aberrance in intestinal microbiota may be a cause, result or both of allergic diseases. Nevertheless, a normalization of the intestinal microbiota may be effective for the treatment of allergic diseases. In fact, recent clinical studies have provided evidence that probiotic supplementation indeed has an effect on allergic diseases. Isolauri *et al.* studied the treatment of atopic eczema with probiotics in infants who developed eczema during exclusive breastfeeding.¹⁸ The infants were weaned to a probiotic supplemented hydrolyzed formula. After 2 months of treatment, the SCORAD score was significantly lower in infants who received either *Bifidobacterium lactis* Bb-12- or *Lactobacillus rhamnosus* GG-supplemented formula than in infants who received unsupplemented hydrolyzed formula. The same authors also showed that the clinical score of atopic dermatitis improved significantly during a 1-month study period in infants with food allergy treated with *Lactobacillus rhamnosus* GG supplemented hydrolyzed formula.¹⁹ Rosenfeldt *et al.* demonstrated that a combination of *Lactobacillus rhamnosus* 19070-2 and *Lactobacillus reuteri* DSM 122460 given for 6 weeks to 1 to 13-year-old children with atopic dermatitis resulted in a more efficient improvement of eczema, al-

Table 1 Prevalence of certain species of intestinal microorganisms in healthy and allergic children

Microorganisms	Prevalence (%) (Healthy/Allergic)			
	1 week	1 month	3 months	12 months
Enterococci	96/67*	96/72*	96/89	96/89
Lactobacilli	8/39*	46/56	34/56	38/44
Bifidobacteria	50/17*	69/39	62/28*	69/22*

*Statistically significant difference (modified from ref. 14)

**Fig. 2** Ratios of *Bacteroides* to *Bifidobacterium* in allergic and healthy children at 2 years of age

though the total SCORAD index did not change in the whole group.²⁰ They also recently reported that *Lactobacillus* supplementation leads to a significant decrease in the frequency of gastrointestinal symptoms in food-allergic patients with atopic dermatitis.²¹

Several studies on the effects of probiotics on allergic rhinitis have been reported. Wang *et al.* assessed whether the ingestion of fermented milk containing *Lactobacillus paracasei*-33 (LP-33) can improve the quality of life of patients with perennial allergic rhinitis in a randomized, double-blind, placebo-controlled trial. The results suggest that the ingestion of LP-33-fortified fermented milk for 30 days can effectively and safely improve the quality of life of patients with allergic rhinitis.²² In contrast, Helin *et al.* reported no significant effect of probiotic bacteriotherapy with *Lactobacillus rhamnosus* GG in teenagers and young adults who were allergic to birch pollen and apple food and had intermittent symptoms of atopic allergy and/or mild asthma.²³

The effects of probiotics in the prevention of early atopic disease in children at high risk, *i.e.* with a family history of atopy, were also studied.²⁴ *Lactobacillus rhamnosus* GG was given in capsules to mothers daily for 24 weeks before the expected date of delivery,

and, after delivery, either to breastfeeding mothers or children (capsule content mixed with water and given with a spoon) for 6 months. Most families gave the capsules to the infants. In a prospective study from birth, atopic eczema was diagnosed in 46 of 132 (35%) children at 2 years of age. The frequency of atopic eczema in the probiotic group was half that of the placebo group (15/64 [23%] *vs.* 31/68 [46%]; relative risk 0.51 [95% CI 0.32–0.84]). Of special note, no differences in skin prick test positivity or total or specific IgE levels were observed between the placebo and probiotic groups. These children were evaluated again at 4 years of age, and atopic eczema was diagnosed on the basis of a questionnaire and clinical examination.²⁵ Fourteen of 53 children who received *Lactobacillus rhamnosus* GG had developed atopic eczema compared with 25 of 54 children in the placebo group, a relative risk of 0.57 and a 95% CI of 0.33–0.97. Again, no differences in skin prick test reactivity were found between the groups. Another study indicated that the long-term consumption of milk containing *Lactobacillus rhamnosus* GG reduces respiratory infections in children attending daycare centers.²⁶ Recently, it was reported that repeated oral application of a non-pathogenic *Escherichia coli* strain in the early postnatal period prevented the incidence of allergies over a long-term (10 and 20 years) study.²⁷ These data suggest that infants are the main targets for probiotic treatment for the prevention of allergic diseases.

EFFECTS OF PROBIOTICS ON INNATE IMMUNE FUNCTION

Studies on the effects of probiotic treatment for allergic diseases have demonstrated that cytokine production can be modified by probiotics. Two types of upregulation of cytokine production have been shown: Th1 type cytokines such as IFN- γ and regulatory cytokines such as interleukin (IL) 10 or transforming growth factor beta (TGF- β). Pohjavuori *et al.* reported that *Lactobacillus rhamnosus* GG raises IFN- γ production of PBMC in infants with cow's milk allergy and in infants with IgE-associated dermatitis.²⁸ Aldinucci *et al.* gave rhinopathic patients either yoghurt or partially skimmed milk for 4 months and compared cytokine production between the two groups. They found that cultured

PBMC from the group fed yoghurt released more IFN-gamma and less IL-4 compared with the control group.²⁹ Interestingly, plasma cytokine levels remained at basal levels. Rosenfeldt *et al.* also could not find any change in serum IFN-gamma levels despite an improvement in atopic dermatitis by treatment with *Lactobacillus rhamnosus* 19070-2 and *Lactobacillus reuteri* DSM 122460.²⁰ Rautava examined the amount of TGF-beta2 in the milk of mothers receiving or not receiving probiotics, and its relationship to the risk of infants developing atopic eczema during the first 2 years of life. They found that TGF-beta2 levels in the breast milk of mothers receiving probiotics were higher than in mothers receiving placebo, and that infants whose mothers received probiotics had a significantly lower risk of developing atopic eczema than infants whose mothers received the placebo.³⁰ The same group also showed that oral *Lactobacillus rhamnosus* GG ingestion for 5 days to 4 weeks could alleviate the clinical symptoms of gastrointestinal inflammation and atopic dermatitis, an effect that is associated with elevated serum levels of IL-10.³¹ These data suggest that probiotics increase both Th1 and regulatory cytokines.

Cytokine production from T lymphocytes in the adaptive immune system is controlled by innate immunity. Thus, the effect of probiotics on innate immunity, such as macrophage and dendritic cells (DCs), has been studied. The stimulation of human mononuclear cells with *Lactobacillus rhamnosus* GG has been shown to promote the production of IFN-gamma, IL-12 and IL-18, the latter two being monocyte-specific cytokines.³² When the mechanisms of activation were studied in human monocytes, the activation of NF- κ B and STAT was shown after stimulation with *Lactobacillus rhamnosus* GG cell wall components.³³ However, pathogenic bacteria were also found to stimulate macrophage/DC to produce inflammatory cytokines in an *in vitro* study.³⁴ Thus, the differences in the innate immune responses to probiotics and pathogenic bacteria are not yet fully clear. Furthermore, different *Lactobacillus* species differ in their ability to induce cytokine expression. *Lactobacillus casei* is a strong inducer of IL-12, IL-6 and TNF-alpha together with maturation surface markers. In contrast, *Lactobacillus reuteri* appears to be a poor IL-12 inducer and inhibits cytokine induction and up-regulation of B7-2 induced by other *Lactobacillus* species.³⁵ We examined cytokine production by cord blood monocytes following stimulation with either *Bifidobacterium adolescentis* or *Bifidobacterium bifidum*. The results showed that the cytokine-inducing activities of these two *Bifidobacterium* species differ (Fig. 3). These findings strongly suggest that different species/strains in probiotics may modify the function of monocyte/DCs differently, and thus modify the characteristics of the immune response that is triggered.

INTERACTION OF PROBIOTICS WITH EPITHELIAL CELLS

Intestinal epithelial cells play an important role in the presentation of oral antigens and also in the regulation of intestinal immune responses. Intestinal microbiota have been suggested to be important regulators of the function and development of immune and epithelial cells. Usually, commensal microbiota coexist peacefully with us and no inflammation is evoked, while the presence of virulence factors on pathogenic bacteria amplifies inflammatory immune responses. Although regulatory mechanisms driven by CD4 + regulatory T cells in the lamina propria are important for maintaining tolerance to enteric bacteria,³⁶ it is likely that other equally important mechanisms controlling innate immunity and inflammation operate at the level of epithelial cells. Mice deficient in MyD88, the adapter molecule essential for TLR signaling, fail to express epithelial hsp25 and hsp72 and are highly susceptible to experimental inflammatory bowel disease (IBD) initiated by dextran sodium sulfate, suggesting that through TLR signaling, bacterial flora may help protect the gut epithelium from nonspecific damage.³⁷ It has been shown that normal flora induce the cytoprotective proteins hsp25 and hsp72 in colonic epithelial cells.³⁸ Nonpathogenic microorganisms in the gut have also been shown to regulate inflammation negatively in other ways.^{39,40} Kelly *et al.* showed that the nonpathogenic bacterium, *Bacteroides thetaiotaomicron* targets the transcriptionally active NF- κ B subunit RelA leading to the activation of the peroxisome proliferator activated receptor (PPAR) and a PPAR-dependent anti-inflammatory mechanism.³⁹ Interestingly, *Bacteroides vulgatus* did not produce a similar effect, suggesting a strain difference. Neish *et al.* showed that avirulent *Salmonella* inhibit the activation of NF- κ B in epithelial cells by blocking the polyubiquitination of phosphorylated I κ B,⁴⁰ while enteropathogens induce NF- κ B activation of epithelial cells leading to inflammation.⁴¹ These data indicate commensal microbiota have machinery different from enteropathogenic bacteria to allow them to coexist with us. In addition to the mechanisms described above, several other functions have been reported. For example, commensals may play a role in the recovery of intestinal epithelia as suggested by a report on the prevention of cytokine-induced apoptosis in intestinal epithelial cells in the presence of *Lactobacillus rhamnosus* GG.⁴² This kind of protection against inflammation-induced injury may be important in the regulation of the intestinal immune response when new antigens are encountered during infancy, or in inflammatory conditions induced by pathogenic microbes and allergens.

CONCLUSION

How probiotics exert their effects on innate immunity

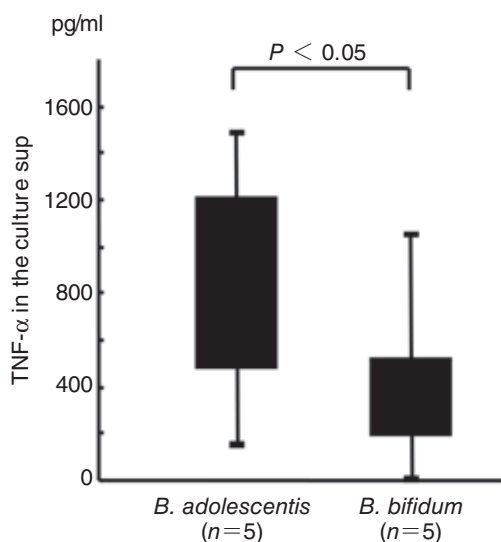


Fig. 3 Difference in cytokine-inducing activity of *Bifidobacterium adolescentis* and *Bifidobacterium bifidum*. Cord blood monocytes were cultured with heat-inactivated bacteria for 24 hours, and TNF- α in the culture supernatant was measured using a commercial ELISA kit.

remains an open question, although accumulating evidence indicates that probiotics may be an alternative option for the treatment of allergic diseases. More precise information is needed about the interaction between commensal microbiota and the innate immune system. Macrophages and DCs obtain information from residential cells in the tissue. It is likely that probiotics act on the innate immune system through residential cells, such as epithelial cells, rather than by interacting directly with macrophages and DCs. A recent study has indicated that epithelial cells and stromal cells in the intestine exert a profound suppressive effect on intestinal macrophages through the production of TGF- β as well as IL-10.⁴³ Future studies will focus on the effects of probiotics on epithelial cells and stromal cells.

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