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Clinical efficacy and mechanism of probiotics in allergic diseases

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A complex interplay between genetic and environmental factors partially contributes to the development of allergic diseases by affecting development during prenatal and early life. To explain the dramatic increase in the prevalence of allergic diseases, the hygiene hypothesis proposed that early exposure to infection prevented allergic diseases. The hygiene hypothesis has changed to the microbial hypothesis, in which exposure to microbes is closely linked to the development of the early immune system and allergic diseases. The intestinal flora may contribute to allergic disease through its substantial effect on mucosal immunity. Based on findings that exposure to microbial flora early in life can change the Th1/Th2 balance, thus favoring a Th1 cell response, probiotics may be beneficial in preventing allergic diseases. However, evidence from clinical and basic research to prove the efficacy of probiotics in preventing allergy is lacking. To date, studies have yielded inconsistent findings on the usefulness of probiotics in allergic diseases. It is difficult to demonstrate an exact effect of probiotics on asthma, allergic rhinitis, and food allergy because of study limitations, such as different first supplementation period, duration, different strains, short follow-up period, and host factors. However, many studies have demonstrated a significant clinical improvement in atopic dermatitis with the use of probiotics. An accurate understanding of the development of human immunity, intestinal barrier function, intestinal microbiota, and systemic immunity is required to comprehend the effects of probiotics on allergic diseases.

Key words: Allergy, Hygiene hypothesis, Immunity, Microbiota, Probiotics

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Introduction

The Developmental Origins Hypothesis for Health and Disease proposes that all organ systems undergo developmental programming in utero that predetermines subsequent physiologic and metabolic adaptations during adult life[1)]. Exposure to environmental factors during prenatal and early life can contribute to the development of allergic diseases, which affect human health later in life[2)]. The rapid increase in the prevalence of allergic diseases and the high burden requires the development of new strategies for effective prevention, diagnosis, and treatment. In this regard, the hygiene and microbial hypothesis may be helpful. Because exposure to microbial flora early in life can change the balance of immune development, probiotics may be beneficial in preventing allergic diseases. In this article, we review the evidence supporting the hygiene hypothesis and the mechanisms of action of probiotics based on this hypothesis. We summarize recent clinical and basic research to elucidate the mechanisms of probiotics and their effects on allergic diseases.

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From the hygiene hypothesis to the microbial hypothesis

The hygiene hypothesis was proposed more than 20 years ago by Strachan to explain the dramatic increase in the prevalence of allergic diseases over the past few decades[3]. The original hygiene hypothesis proposed that early exposure to infection through contact with older siblings prevented allergic diseases[3,4]. Later, the hygiene hypothesis was extended to explain the great increase in the prevalence of Th1 diseases, such as inflammatory bowel diseases and autoimmune diseases, that occurred over the same period[5]. However, the exact scientific underpinning for the hygiene hypothesis, for example, a specific infection that can prime the immune system to prevent disease, is an unsolved puzzle.

Several studies report a consistently low prevalence of allergies in farmers' children[4]; it remains unclear which specific factors are most important, but microbial exposure may play a role through the inhalation of endotoxin[6]. Endotoxin, a lipopolysaccharide present in the outer membrane of gram-negative bacteria, downregulates Th2 cytokine production[7]. However, in inner-city communities, domestic endotoxin exposure was positively associated with wheeze in children at 2 years of age[8]. One unanswered question is whether the greater levels of endotoxin associated with an inner-city lifestyle can explain the higher prevalence of asthma relative to that observed in rural areas.

Some studies have recently revisited the hygiene hypothesis and suggested that the decline in childhood infections is less important than how modern societal practices caused the disappearance of ancestral indigenous microbiota species that might confer benefits beyond our current understanding[9]. Initial studies of allergic diseases focused on gut microbiota. Allergic diseases among children are partially associated with differences in their intestinal microflora in countries with a low (Estonia) and high (Sweden) prevalence of allergies[10]. Evidences collected over the last few decades from human and mouse studies indicate that colonization of the gut early in life plays a substantial role in directing immune system development. Therefore, we need to understand the importance of gut colonization early in life and to determine whether altering microbial exposures during the perinatal period promotes lifelong dysregulated immune responses. In a mouse model, the intestinal bacterial flora was shown to play a crucial role in oral tolerance induction, probably by affecting the development of the immune system at the neonatal stage[11].

After birth, the diversity of the gut microbiome increases with age[12]. A healthy human fetus is thought to develop within a bacteria-free environment. Upon birth, a neonate is exposed to a wide variety of microbes, many of which are encountered during and after passage through the birth canal. The latter comprises an ecosystem heavily colonized by a relatively limited set of bacterial taxa[13]. Vaginally delivered infants acquire bacterial communities resembling their mother's vaginal microbiota, which is dominated by *Lactobacillus, Prevotella,* or *Sneathia* spp., while infants delivered by caesarian section harbor bacterial communities similar to those found on the skin surface, which are dominated by *Staphylococcus, Corynebacterium*, and *Propionibacterium* species[14].

Microbial exposure during the perinatal period is linked to the epigenetic regulation of genes involved in allergic inflammation, and it alters susceptibility to allergic diseases[15]. The emerging understanding of the importance of microbial contact during the fragile periods of fetal life, delivery, and infancy in healthy immune and metabolic programming, creates new opportunities to improve infant health and reduce the risk of disease in later life. According to the basis of the hygiene hypothesis, the microbial inhabitants of the human affect the early development of the immune system. This concept led us to investigate the probiotics-induced modulation of mechanisms underlying the development of allergic diseases.

Clinical efficacy of probiotics on allergic diseases

1. Asthma

1) What is known

Antibiotics enhance allergic airway responses in experimental animals by altering the intestinal microbiota, and probiotics modulate allergic responses in the lower respiratory tract[16-20]. In a double-blind, placebo-controlled study, 1,223 mothers with infants at high risk for allergy received a probiotic mixture (*Bifidobacterium* spp. and *Propionibacteria* spp.) or placebo during the last few months of pregnancy, and their infants received the same mixture from birth until 6 months of age. However, a preventive effect of probiotics on asthma was not observed up to 5 years of age[20]. In 2 other double-blind, placebo-controlled, randomized trials with infants at risk of allergy, probiotic supplementation failed to decrease the frequency of wheezing at 1 year and influence asthma prevalence rates at 2 years[21,22]. Supplementation with probiotics was associated with an increased rate of recurrent episodes of wheezy bronchitis[23] but not with a reduced prevalence of inhalant allergen sensitization[24]. Probiotics prevented asthma-like symptoms in infants with atopic dermatitis[25], whose pulmonary function and peak expiratory flow rates decreased significantly. In addition, the clinical symptom scores for asthma and allergic rhinitis decreased in the probiotic-treated patients[26]. Oral administration of probiotics attenuated the symptoms of allergic asthma in a

mouse model, induced immune regulation by a CD4(+)CD25(+) Foxp3(+) regulatory T (Treg) cell-mediated mechanism[16], and effectively suppressed airway hyperresponsiveness[2].

2) Future studies

Although the possibility of asthma prevention and treatment is indicated by research on animal models, no primary prevention study demonstrates an effect of probiotic supplementation in humans. Despite numerous studies, demonstration of an effect of probiotics has been impeded by limitations, such as different first supplementation periods, duration of supplementation, and short follow-up periods. To overcome these limitations, future studies should be conducted on larger numbers of subjects and for longer duration.

2. Allergic rhinitis

1) What is known

Immune responses in the gut may modulate immune responses in distant target organs, including the nose[18,27]. Probiotics alleviated nasal symptoms, prevented the pollen-induced infiltration of eosinophils into the nasal mucosa[28], and modulated Th2-skewed immune responses in allergic rhinitis[29].

Probiotics alleviated perennial and seasonal allergic rhinitis. In a study of preschoolers treated with probiotics or placebo for 12 months, there was a difference in the cumulative incidence of rhinitis episodes[30]. In adult patients with seasonal allergic rhinitis, probiotics modulated immune responses; they have the potential to alleviate the severity of symptoms[31]. However, other studies showed that probiotics provided few clinical benefits and did not alleviate the symptoms or reduce the use of medication[32,33].

2) Future studies

The heterogeneity of studies on the effects of probiotics in allergic rhinitis precludes meta-analysis. Unlike in other allergic diseases, the therapeutic effect of probiotics in allergic rhinitis has been primarily demonstrated, whereas their preventive effects have not been conclusively defined. Evidence indicates that allergic rhinitis may be subdivided into several phenotypes (perennial allergic rhinitis, seasonal allergic rhinitis, and Japanese cedar pollen-induced allergic rhinitis). Well-designed future studies that consider theses phenotypes of allergic rhinitis will help us to understand the effects of treatment on allergic rhinitis.

3. Atopic dermatitis

1) What is known

There are numerous studies on the efficacy of probiotics for the prevention and treatment of atopic dermatitis[34,35] (Fig. 1). A Cochrane review showed that there was insufficient evidence to recommend the addition of probiotics to infant diets for the prevention of atopic dermatitis[36]. In contrast, there is convincing evidence that probiotics effectively prevent and treat adult and childhood atopic dermatitis[37,38].

In most studies reporting beneficial effects, mothers received probiotics during pregnancy and their babies continued with the same product after birth. The preventive effects of probiotics on eczema were greater in infants with a family history of allergic diseases[22,39,40].

A Korean population based study showed that prenatal and postnatal supplementation with a probiotic mixture effectively prevented the development of eczema in infants at high risk of allergy during the first year of life[41]. According to a review article, various meta-analyses and systematic reviews show that probiotics can prevent the development of atopic dermatitis, particularly in infants who were administered probiotics perinatally[42]. A study of probiotic supplementation in Korean adults with atopic dermatitis showed modified production of cytokines from the peripheral blood mononuclear cells of these patients[35].

Oral administration of probiotics prevented the development of atopic dermatitis in a novel mouse model by suppressing the production of the inflammatory cytokines; interleukin (IL)-4 and thymic stromal lymphopoietin (TSLP) in the skin through a mechanism that may involve CD4(+)CD25(+)Foxp3(+)

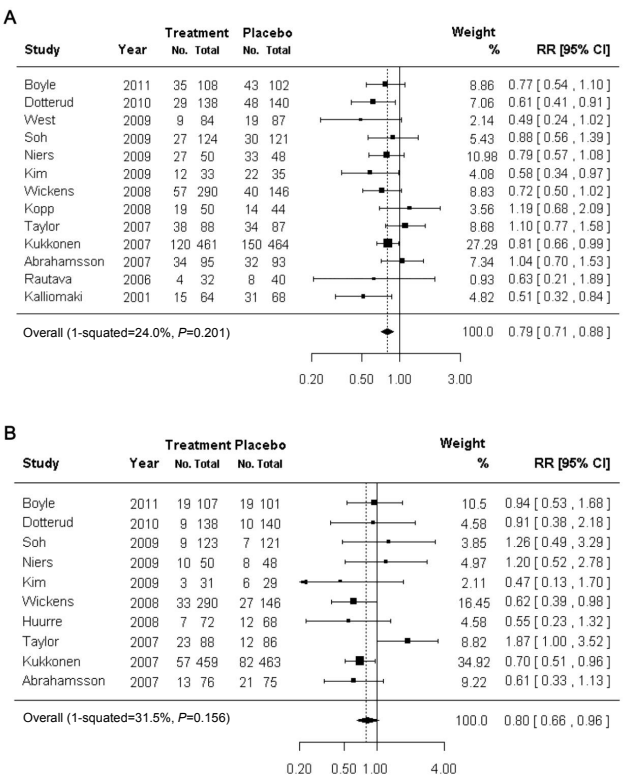

Fig. 1. Usefulness of probiotics in the prevention of atopic dermatitis. The preventive effect of probiotics on atopic dermatitis (A) and immunoglobulin E-associated atopic dermatitis (B). RR, relative risk; CI, confidence interval. Reproduced from Pelucchi C, et al. Epidemiology 2012;23:402-14, with permission of Lippincott Williams & Wilkins, Inc.[17].

Treg cells[43]. Oral administration of *Lactobacillus* strains suppressed house-dust mite dermatitis in the NC/Nga mouse, a representative animal model of human atopic dermatitis[44]. A meta-analysis of the effect of probiotics on atopic dermatitis suggested that probiotics may be effective for preventing atopic dermatitis in high-risk infants. There is, however, insufficient evidence for giving probiotics to all pregnant women and their babies to prevent allergic diseases.

2) Future studies

The authors of the Cochrane review advised caution in interpreting the results of their meta-analysis because of heterogeneity and high rates of follow-up loss (17–61%) in individual trials[45]. There is insufficient evidence that probiotics are clinically effective for treating atopic dermatitis; however, the suggestion that probiotics may be effective for preventing atopic dermatitis can be accepted under limited conditions. An accurate understanding of the development of human immunity, intestinal barrier function, intestinal microbiota, and systemic immunity is required to evaluate the effects of probiotics on allergic diseases such as atopic dermatitis. Further basic research into the roles and functions of probiotics will be required.

4. Food allergy

1) What is known

There are very few studies of probiotic treatment for food allergy, and no systematic review seems possible at present. Moreover, most of the clinical information regarding probiotics and food allergy is derived from studies of patients with atopic dermatitis. The therapeutic oral administration of probiotics suppressed the skewed Th2 response in allergic mice and protected against anaphylactic reactions in recent murine models of food allergy[46,47].

In several clinical trials, however, oral supplementation with probiotics did not significantly affect allergic inflammatory markers (total and specific immunoglobulin E) or cytokines; there were no positive therapeutic outcomes (improvement of symptoms and acquisition of tolerance)[48,49].

In studies reporting beneficial therapeutic effects, most infants were exclusively breast-fed or provided an extensively hydrolyzed formula, and the effects reported were related to atopic dermatitis rather than food allergy[50,51]. The most significant improvements were observed when probiotics were used in conjunction with breastfeeding or a hypoallergenic formula.

2) Future studies

To date, studies have yielded inconsistent findings on the efficacy of probiotics for preventing and treating food allergy. These discrepancies may be attributed to variations in multiple factors related to the probiotics (type, dose, mixtures, and duration) or to the recipients (birth method, diet, and age). Therefore, further studies are required to overcome these limitations.

Immunological mechanisms involved in the effects of probiotics on the prevention and treatment of allergic diseases

Accumulating data suggest that certain bacterial strains provide protective signals, while others strains may stimulate aggressive and damaging immune responses. The effects on an individual's microbiota of the continuous administration of probiotics from an early age, which stimulates the immune system, has been considered beneficial by many clinicians and researchers (Fig. 2). However, the results of many studies of allergic diseases are not consistent. In particular, studies of allergic diseases in humans have not established any definite beneficial effects of probiotics. In this section, we discuss the mechanism of action of probiotics and summarize recent clinical data and animal studies on the effects of probiotics on allergic diseases (Table 1).

1. Initial research on the mechanisms of probiotics in allergic diseases

The pathogenesis of allergic diseases was first described as an imbalance of Th1/Th2 cells. Probiotics inhibit allergic diseases by suppressing the Th2 response. Interleukin (IL)-4, IL-5, and IL-13 are representative cytokines released by Th2 cells that are suppressed by probiotics[16,52] (Fig. 3). Further, probiotics increase IL-10 and tumor growth factor (TGF)-β levels by inducing Tregs cells in allergic diseases[52]. However, the results of many studies differ, and they cannot be fully explained by an imbalance of Th1/Th2 responses in the development of allergic diseases. Consequently, the mechanism of probiotics is open to dispute.

2. New insight into the mechanisms of probiotics in allergic diseases

The previously discussed mechanisms of probiotics were

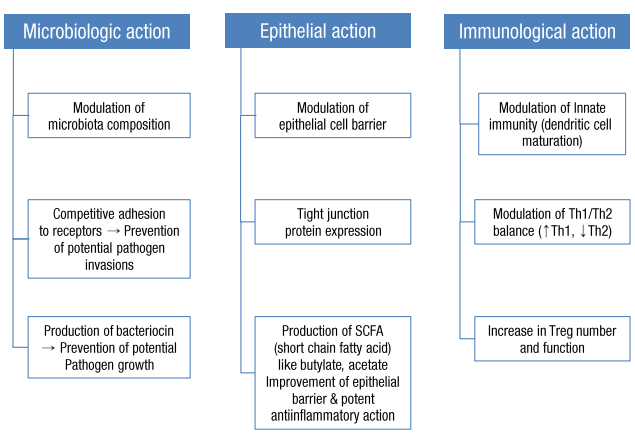

Fig. 2. Effect of probiotics on the intestinal microbiota. SCFA, short chain fatty acid.

Table 1. Recent clinical studies and animal model studies evaluating the efficacy of probiotics in Korea

	Year	Author	Title	Subjects/model	Journal name
Human	2010	Kim et al.[41]	Effect of probiotic mix (*Bifidobacterium bifidum, B. lactis, Lactobacillus acidophilus*) in the primary prevention of eczema: a double-blind, randomized, placebo-controlled trial	112 Pregnant women with a family history of allergic diseases and their 68 infants at 1 year	Pediatr Allergy Immunol
	2008	Lee et al.[57]	The immunologic effects of *Lactobacillus rhamnosus* (Lcr35) supplements in adult patients with atopic dermatitis	5 Adults with AD	Korean J Asthma Allergy Clin Immunol
	2007	Kong et al.[58]	The effects on treatment of atopic dermatitis with oral lactobacillus casei supplements in Korean children	44 Children with AD	Pediatr Allergy Respir Dis
Animal	2012	Jang et al.[16]	Asthma prevention by *Lactobacillus rhamnosus* in a mouse model is associated with CD4(+)CD25(+)Foxp3(+) T cells	Asthma mouse model	Allergy Asthma Immunol Res
	2012	Kim et al.[43]	A novel mouse model of atopic dermatitis with epicutaneous allergen sensitization and the effect of *Lactobacillus rhamnosus*	AD mouse model	Exp Dermatol
	2011	Won et al.[44]	Oral administration of *Lactobacillus* strains from Kimchi inhibits atopic dermatitis in NC/Nga mice	AD mouse model	J Appl Microbiol
	2010	Yu et al.[59]	The effects of *Lactobacillus rhamnosus* on the prevention of asthma in a murine model	OVA-induced asthma mouse model	Allergy Asthma Immunol Res
	2010	Hong et al.[60]	Differential suppression of heat-killed lactobacilli isolated from Kimchi, a Korean traditional food, on airway hyper-responsiveness in mice	OVA-induced asthma mouse model	J Clin Immunol
	2008	Kim et al.[61]	Effect of oral probiotics (*Bifidobacterium lactis* AD011 and *Lactobacillus acidophilus* AD031) administration on ovalbumin-induced food allergy mouse model	OVA-induced allergy mouse model	J Microbiol Biotechnol
	2008	Choi et al.[62]	The effect of *Lactobacillus acidophilus* on the primary prevention of asthma in a murine asthmatic model	OVA-induced asthma mouse model	Pediatr Allergy Respir Dis
	2008	Park et al.[63]	New functional probiotic *Lactobacillus* sakei probio 65 alleviates atopic symptoms in the mouse	AD mouse model	J Med Food
	2005	Kim et al.[35]	Oral probiotic bacterial administration suppressed allergic responses in an ovalbumin-induced allergy mouse model	OVA-induced allergy mouse model	FEMS Immunol Med Microbiol

AEDS, atopic eczema-dermatitis syndrome; AD, atopic dermatitis; OVA, ovalbumin.

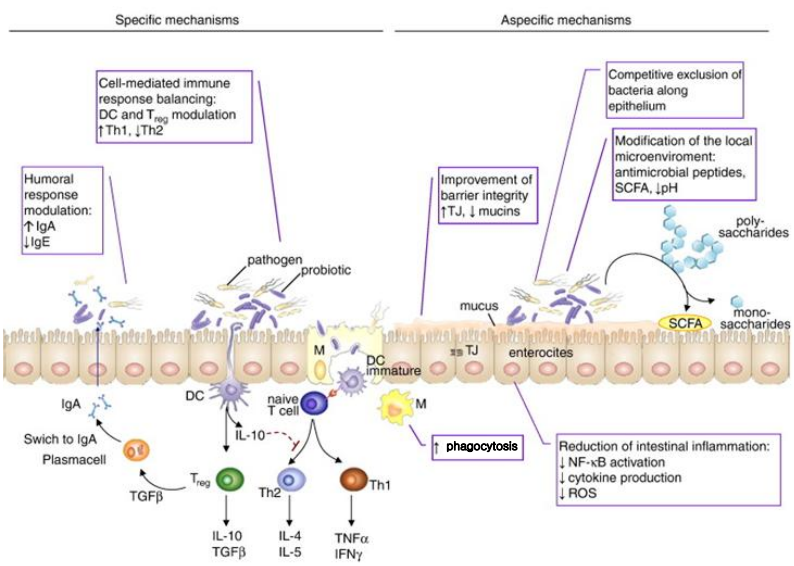

Fig. 3. Immune mechanisms of probiotics. DC, dendritic cells; TJ, tight junction; SCFA, short chain fatty acid; IgA, immunoglobulin A; IgE, immunoglobulin E; IL, interleukin; TNF, tumor necrosis factor; IFN, interferon; NF-κB, nuclear factor-κB; ROS, reactive oxygen species. Reproduced from Iacono A, et al. J Nutr Biochem 2011;22:699-711, with permission of Elsevier Inc.[10].

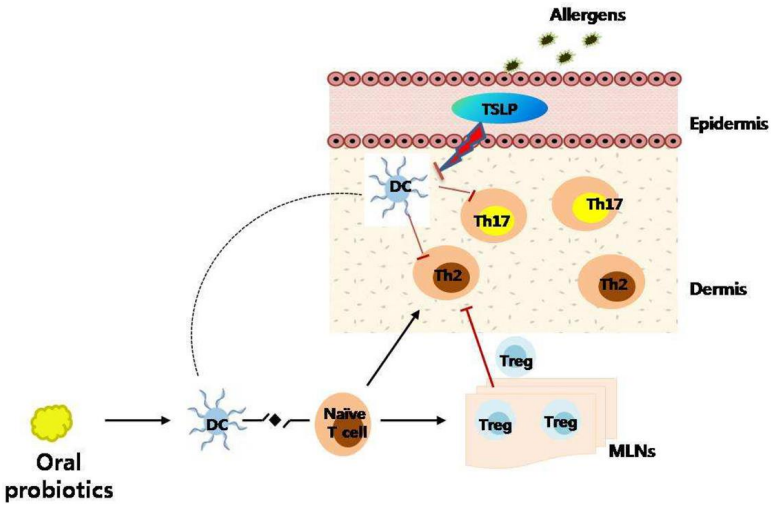

Fig. 4. Proposed mechanism of probiotics in an animal model of atopic dermatitis. Exposure to allergens on atopic skin increases the expression of thymic stromal lymphopoietin (TSLP) in the skin. TSLP-stimulated dendritic cells (DCs) induce naive T cells to differentiate into Th2 cells and Th17 cells, which induce allergic inflammation in the skin. Oral probiotics might inhibit these processes by increasing the number of regulatory T (Treg) cells in mesenteric lymph nodes. Tregs cells then migrate to the skin from the lymph nodes through lymphatic drainage, and suppress Th2 and Th17 responses (⊥) in the skin. Tregs cells also suppress the expression of TSLP in the skin (⊥). MLNs, mesenteric lymph nodes.

superseded following the discovery of a novel paradigm in the development of allergic diseases. Th17 cells induce allergic inflammation in a mouse model of asthma[53]; probiotics suppressed this inflammation[52]. Probiotics suppressed interferon-γ (Th1-related cytokines), IL-4 (Th2-related cytokines), and Th17 cells in splenic CD4 T cells and increased the expression of IL-10 and TGF-β (Treg-related cytokines) in mesenteric lymph nodes[54]. Our own studies using a mouse model of atopic dermatitis demonstrated the suppression of the Th17 response in the skin following the administration of probiotics (Fig. 4).

The influence of probiotics on T cell differentiation suggests that dendritic cells (DCs) play an important role in the mechanism of action of probiotics in allergic diseases[54,55]. Thus, it is reasonable to conclude that probiotics inhibit naive T cell differentiation to Th2 cells. Moreover, probiotics inhibit the differentiation of mature DCs *in vitro*[54,55]. However, very few in vivo studies of allergic diseases have demonstrated a relationship between mature DCs and probiotics. In addition, some studies have shown this effect only in tumors[19]. Our research confirms that DCs are involved in the suppression of asthma by probiotics following the transfer of mature DCs in mice[56].

TSLP plays an important role in the DC-mediated differentiation of T cells[55]. We are focusing on how Th2, Th17, and Treg cells along with TSLP influence the effects of probiotics on allergic diseases. However, further studies are needed to identify the additional mechanisms of probiotics on allergic diseases in humans and animal models.

Conclusions

Examining interactions between microorganisms in the environment, microorganisms in the mucosa, and humans and assessing how microorganisms modulate immune responses may be an interesting new approach in studying human diseases caused by chronic inflammation. The interactions between probiotics and the immune system might be beneficial for preventing allergic disease; however, evidence is lacking to support this conclusion. Moreover, the advent of the microbial hypothesis has raised new concerns about the association between immune responses and human gut microbiota and the impact of this association on the development of allergic diseases. Future research based on extending this concept may help to improve the efficacy of probiotics for preventing and treating allergic diseases, particularly atopic dermatitis. Confirmation of the association between the gut microbiota and the development of allergic diseases in humans awaits future research.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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