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Review Article

Gut microbiota and allergic diseases in children

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Abbreviations:
BAPB, butyric acid-producing bacteria; CD, Crohn's disease; CFU, colony forming unit; FMT, fecal microbiota transplantation; GPR, G protein-coupled receptor; IBD, inflammatory bowel disease; IQR, interquartile range; RCT, randomized controlled trial; rRNA, ribosomal RNA; SCFA, short-chain fatty acids; UC, ulcerative colitis

ABSTRACT

The gut microbiota resides in the human gastrointestinal tract, where it plays an important role in maintaining host health. The human gut microbiota is established by the age of 3 years. Studies have revealed that an imbalance in the gut microbiota, termed dysbiosis, occurs due to factors such as cesarean delivery and antibiotic use before the age of 3 years and that dysbiosis is associated with a higher risk of future onset of allergic diseases. Recent advancements in next-generation sequencing methods have revealed the presence of dysbiosis in patients with allergic diseases, which increases attention on the relationship between dysbiosis and the development of allergic diseases. However, there is no unified perspective on the characteristics on dysbiosis or the mechanistic link between dysbiosis and the onset of allergic diseases. Here, we introduce the latest studies on the gut microbiota in children with allergic diseases and present the hypothesis that dysbiosis characterized by fewer butyric acid-producing bacteria leads to fewer regulatory T cells, resulting in allergic disease. Further studies on correcting dysbiosis for the prevention and treatment of allergic diseases are warranted.

Introduction

In the human body, more than 40 trillion bacteria of approximately 1000 species reside in the intestines, oral cavity, respiratory tract, skin, and genitourinary tract. There are bacterial microbiota in each location, but most bacteria reside in the intestines.[1,2] Recently, due to advances in next-generation sequencing methods, the precise characteristics of microorganisms comprising the gut microbiota have been revealed. The gut microbiota encodes over three million genes that can produce various metabolites.[3] Studies focusing on the gut microbiota have revealed that it plays an important role in human health by modulating host immune defenses and regulating host metabolism and brain function. Imbalance in the gut microbiota, called dysbiosis, during early life is associated with the development of various diseases later in life including allergic diseases,[4–6] inflammatory bowel disease (IBD),[7,8] irritable bowel syndrome,[9] necrotizing enterocolitis,[10] diabetes,[11] obesity,[12,13] cardiovascular disease,[14] autism spectrum disorder,[15] and sudden infant death syndrome.[16] In fact, several studies have focused on the relationship between dysbiosis and the development of allergic diseases.

In this review, we discuss factors affecting the gut microbiota in children and characteristics of dysbiosis in children with allergic diseases based on the latest studies, including our own. We present a hypothesis on how dysbiosis might be related to the onset of allergic diseases and discuss approaches to prevent or treat dysbiosis.

Development of the gut microbiota

Previously, the fetus was considered to not have any gut microbiota because the intrauterine environment is sterile. However, the current understanding is that the human gut microbiota

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begins to become established in fetal life, based on several studies reporting the existence of bacterial DNA in the placenta,[17] amniotic fluid,[18] and meconium of children born by cesarean section.[19]

Furthermore, the maternal gut microbiota might determine the transcriptional profile of the fetal intestinal microbiota.[20] Importantly, children born through vaginal delivery acquire abundant bacteria residing in the vagina and perianal area, which accelerates the establishment of the gut microbiota. According to a study evaluating the quantity of bacteria in the gut microbiota after birth, there are 10^7 bacteria per gram of stool on day 1 of life, which increases to 10^9 per gram on day 3, 10^{10} per gram on day 7, and 10^{11} per gram by 6 months, which is almost the level in adults.[21] In addition, the composition of the gut microbiota changes greatly after birth. Odamaki *et al.* analyzed stool samples of 367 healthy Japanese individuals aged 0–104 years using 16S ribosomal RNA (rRNA) sequencing and found age-dependent changes in the gut microbiota.[22] The dominant phylum in the adult gut microbiota was Firmicutes, including Lactobacillales and Clostridiales, while it was Actinobacteria, including Bifidobacteriales, in the gut microbiota of 1-year-olds. The proportion of Actinobacteria decreases after weaning, changing towards an adult-like gut microbiota by the age of 3 years. The microbiota established by the age of 3 years is maintained through adulthood. Importantly, dysbiosis that develops during the early stages of life may remain into adulthood.[23] Therefore, it is important to establish a favorable gut microbiota during infancy.[24]

Factors affecting the gut microbiota in children

Maternal microbiota from the vagina and intestines,[25,26] mode of delivery,[27–30] feeding type,[27–29] use of antibiotics[29,31,32] and other drugs,[33,34] gestational age,[35] siblings and pets,[36] and regional differences, including diet and sanitary conditions,[37] are factors that affect the gut microbiota of newborns and infants. Here, we discuss the current evidence regarding the effects of these factors on the gut microbiota in children, primarily focusing on the mode of delivery and antibiotic use.

Mode of delivery and the gut microbiota in children

We compared the gut microbiota of 36 newborns according to their mode of delivery using stool samples collected 4 days after birth through 16S rRNA sequencing.[30] There was a higher proportion of bacteria belonging to the orders Bacteroidales and Enterobacteriales. Bacteria in the orders Bacillales and Lactobacillales were less abundant in children born via vaginal delivery compared to children born via cesarean section. Differences in bacteria acquired at birth or immediately after birth leads to large differences in the gut microbiota during the early neonatal period. Bacteria belonging to the orders Bacteroidales and Enterobacteriales include bacteria residing in the vagina or intestines, while Bacillales and Lactobacillales include bacteria residing on the skin or in the oral cavity. One study reported that differences according to the mode of delivery become smaller by 8 months.[38] However, Fouhy *et al.* reported reduced relative abundance of the families Clostridiaceae, Lachnospiraceae, and Ruminococcaceae in children at the age of 4 years who were delivered by cesarean section.[39] Similarly, Salminen *et al.* found decreased abundance of *Clostridia* in children delivered by cesarean section at the age of 7 years,[40] suggesting the possibility that the mode of delivery has a long-lasting effect on the gut microbiota.

Antibiotic use and the gut microbiota in children

Although it is commonly assumed that antibiotics drastically affect the gut microbiota, its actual effect was initially reported by Dethlefsen *et al.* in 2008.[41] Subsequently, there have been several studies on how the use of antibiotics might affect the human gut microbiota.[31,42–44] The effect varies by study subject type, antibiotic type, duration of administration, and route of administration, leading to no consistent conclusions on the characteristics of the gut microbiota. However, many studies have reported that the diversity of gut microbiota decreases with antibiotic use.[31,42–44]

To investigate the effect of antibiotic use on the gut microbiota in children, we analyzed how the gut microbiota changes over time due to antibiotic use in children aged <3 years (median age, 5.2 months) who were diagnosed with and treated for upper urinary tract infection.[32] Ceftriaxone and cefditoren pivoxyl were administered intravenously and orally during the acute phase of the urinary tract infection for 7 days, respectively. Microbial diversity decreased significantly, with a median Shannon index of 3.0 before antibiotic use compared with 1.2 after antibiotic use. Lactobacillales accounted for almost 80% of the total abundance. The decrease in diversity was reversed by 1–2 months after terminating antibiotic administration, and diversity was maintained at the pre-administration level for at least 6 months.

Studies have reported that decreased diversity and altered bacterial composition recover after antibiotic administration ends, but recovery might not be complete.[41,45] It is important to be aware of the long-term effects of antibiotic use on the gut microbiota and try to use antibiotics appropriately.

Role of the gut microbiota in maintaining human health and the relationship between dysbiosis and disease

The gut microbiota ferments dietary fiber and produces short-chain fatty acids (SCFAs) in the intestine. SCFAs are fatty acids with fewer than six carbohydrates, such as butyric acid, acetic acid, and propionic acid. SCFAs are absorbed from the colon. Butyric acid is used as an energy source by colonic epithelial cells, while acetic acid and propionic acid are absorbed into the portal vein as substrates for energy and lipid production. SCFAs are considered to be an important nutrient for human energy production, but recent omics analysis has shown that they have beneficial effects on host metabolism and the immune system.[46–49] There are several receptors known to sense SCFAs and regulate human metabolism: G protein-coupled receptors (GPRs) (GPR41, GPR43, and GPR109A); olfactory receptor 78 (Olfr78), which is also known as a GPR; and aryl hydrocarbon receptor.[50–52] In addition, the gut microbiota affects the metabolism of vitamins, amino acids (e.g., methionine and tryptophan), melatonin, gamma-aminobutyric acid, bile acids, urea, cholesterol, and drugs.[53–56]

It is not difficult to imagine that dysbiosis can trigger the development of various diseases. Although it is difficult to conclude whether dysbiosis is the cause or the result of a disease, the presence of dysbiosis has been reported in various diseases. A relationship between dysbiosis and disease has been reported for gastrointestinal diseases including inflammatory intestinal disorder,[7,8] irritable bowel syndrome,[9] and necrotizing enterocolitis,[10] as well as allergic diseases,[4–6] diabetes,[11] obesity,[12,13] cardiovascular disease,[14] autism spectrum disorder,[15] and sudden infant death syndrome.[16] We have proposed that dysbiosis

might also be present in children with idiopathic nephrotic syndrome[57,58] and Kawasaki disease.[59]

Dysbiosis and allergic diseases

Risk factors for the onset of allergic diseases

The incidence of allergic and autoimmune diseases is increasing across the world.[60,61] Possible reasons suggested for this increase are excessive improvement in sanitary conditions, mode of delivery, antibiotic use, and a Western style diet. Interestingly, these factors also affect the gut microbiota, indicating that dysbiosis might also be related to the onset of allergic diseases.

Hygiene hypothesis

Strachan *et al.* investigated environmental factors related to the onset of allergic diseases in 17,414 adults born in 1953. They reported that being a member of a bigger family and having more older siblings are associated with a lower risk of allergic diseases, suggesting that a hygienic environment with less exposure to infections may be a risk factor for the onset of allergic diseases, which was called the hygiene hypothesis.[62] Later, several epidemiological studies supported the hygiene hypothesis. Children who were raised on a farm,[63,64] entered a day nursery at an early age,[65,66] or had pets in their house[67] were reported to have a lower incidence of allergic diseases, indicating that exposure to various microorganisms in the environment during the period of drastic changes in the gut microbiota might contribute to a lower risk of having allergic diseases in the future.

Mode of delivery and the prevalence of allergic diseases

Several cohort studies have reported cesarean section as a risk factor for the onset of allergic diseases. In a large-scale cohort study conducted in Sweden with 1,086,378 participants, food allergy was positively related with cesarean delivery with a hazard ratio of 1.21.[68] Similarly, cesarean section was significantly associated with asthma symptoms in childhood (odds ratio, 2.2) and physician-diagnosed atopic dermatitis (odds ratio, 1.9).[69] In two meta-analyses, cesarean section was identified as a risk factor for the onset of asthma.[70,71]

Antibiotic use and the prevalence of allergic diseases

Antibiotic use has also been reported to be a risk factor for the onset of allergic diseases. A birth cohort study in Japan reported that antibiotic use before the age of 2 years is significantly associated with the prevalence of asthma (adjusted odds ratio, 1.72), atopic dermatitis (1.40), and allergic rhinitis (1.65) at the age of 5 years.[72] In a large-scale retrospective cohort with 792,130 participants, the adjusted hazard ratio after an antibiotic prescription in the first 6 months of life was 2.09 for asthma, 1.75 for allergic rhinitis, 1.51 for anaphylaxis, and 1.42 for allergic conjunctivitis, respectively.[73] A meta-analysis also reported that maternal antibiotic use during pregnancy or within 12 months after birth is a risk for atopic dermatitis.[74]

Animal studies on the role of the gut microbiota in allergic diseases

To investigate the role of the gut microbiota in allergic diseases, interesting animal studies have been performed. Importantly, in germ-free mice, the intestinal lymphatic tissues are underdeveloped,[75] there are fewer plasma cells that produce mucosal IgA antibodies[76] and regulatory T cells (Tregs),[77] and Th2 is dominant with elevated plasma IgE levels.[78] These finding leads to our recognition that the gut microbiota greatly affects the maturity and maintenance of the host immune system.

In addition, dysbiosis triggered by administering antibiotics to mice early after birth leads to Th2 dominance[79] and fewer Tregs in the intestinal lamina propria.[80] Furthermore, when probiotics were administered to these mice, plasma IgE levels were restored[78] and food allergen sensitization was suppressed via improvements in intestinal barrier function,[81] suggesting that the gut microbiota in early life plays an important role in the onset of allergic diseases.

Gut microbiota of children with allergic diseases

Although there have been many studies on dysbiosis in children with allergic diseases, no consistent characteristics of dysbiosis or the mechanistic relationship between dysbiosis and allergic diseases have been identified. Recent reports on characteristics of the gut microbiota in children with allergic diseases are shown in Table 1. In children with food allergy, decreased levels of the phylum Bacteroidetes and increased levels of the phylum Firmicutes, increased levels of the families Bacteroidaceae, Clostridiaceae, Lachnospiraceae, Leuconostocaceae, Ruminococcaceae, and Streptococcaceae as well as decreased levels of the genera *Citrobacter*, *Clostridium*, *Dialister*, *Dorea*, *Haemophilus*, *Lactococcus*, and *Oscillospira* have been reported.[4,82,83] In children with atopic dermatitis, decreased levels of the genera *Akkermansia*, *Bacteroides*, *Bifidobacterium*, *Faecalibacterium,* and *Lactobacillus*, and increased levels of the genera *Gemella* and *Rhodotorula* have been reported.[84,85] In children with asthma, decreased levels of the genera *Alistipes*, *Bacteroides*, *Bifidobacterium*, *Collinsella*, *Dialister*, *Dorea*, *Faecalibacterium*, *Flavonifractor*, *Roseburia*, and *Veillonella,* and increased levels of the genera *Escherichia*, *Gemmiger,* and *Streptococcus* have been reported. Both studies claim that levels of the genus *Ruminococcus* either increase or decrease.[86–88]

Several prospective studies have revealed the presence of dysbiosis prior to allergic disease onset, suggesting that dysbiosis is likely to be the cause of allergic diseases. Although further studies are required to understand the preventative effect of correcting dysbiosis on allergic diseases, the effect of dysbiosis on the onset of allergic diseases is becoming widely accepted. Furthermore, we focused on butyric acid-producing bacteria (BAPB) as an underlying mechanistic factor. As shown in bold in Table 1, the proportion of BAPB in the gut microbiota was reported to be lower in four of six studies.

Hypothesis on how fewer BAPB triggers the onset of allergic diseases

We would like to present a hypothesis on how dysbiosis might trigger the onset of allergic diseases. First, when various factors including cesarean delivery and antibiotic use lead to dysbiosis characterized by fewer BAPB, intestinal butyric acid concentrations decrease. The decrease in butyric acid concentration leads to suppression of naïve T-cell differentiation into Tregs. The reduction in Tregs impairs the ability of the immune system to suppress excessive immune responses, which results in the onset of allergic diseases (Fig. 1). Our study[6] and a study reporting that children with butyric acid-rich stool samples at 18 months of age tend to have fewer sensitized allergens support our hypothesis.[89] If this hypothesis is correct, using prebiotics and probiotics to increase BAPB levels and postbiotics that are rich in butyric acid might be novel preventative or therapeutic approaches to allergic diseases. Postbiotics are bioactive compounds produced by or released through the metabolic activity of microorganisms; they exert a beneficial effect on the host.[90]

Table 1
Summaries of studies showing differences in the gut microbiota between healthy children and children with allergic diseases.

Year	First author	Number of patients	Disease and age at outcome	Age at stool sampling	Gut microbial changes			
						Genus	Family	Phylum/class/order
2021	Los-Rycharska[85]	87 (59 FA and/or AD)	FA and/or AD at 0–6 mo	0–6 mo	↓	*Bacteroides*		
					↓	*Lactobacillus*		
					↑	*Gemella*		
2020	Bannier[86]	230 (70 asthma, 114 transient wheezing)	Asthma at 6 y	2–4 y	↓	*Collinsella*		
					↓	*Dorea*		
					↑	*Escherichia*		
					↑	*Gemmiger*		
2019	Simonyte-Sjodin[5]	93 (21 allergic disease at 8 y)	Any allergic disease at 8 y	4, 6, 13 mo; 8 y	↓	*Bacteroides*		
					↓	***Coprococcus***		
					↓	*Enterococcus*		
					↓	***Lachnospira***		
					↓	*Lactobacillus*		
					↓	*Prevotella*		
					↓	***Ruminococcus***		
					↑	*Bifidobacterium*		
2018	Arrieta[88]	97 (27 atopic wheezing at 5 y)	Atopic wheeze at 5 y	3 mo	↓	*Bacteroides*		
					↓	*Bifidobacterium*		
					↑	***Ruminococcus***		
					↑	*Streptococcus*		
2018	Fazlollahi[4]	141 (66 egg allergy)	Egg allergy	3–16 mo	↑		Lachnospiraceae	
					↑		Leuconostocaceae	
					↑		Streptococcaceae	
2018	Savage[82]	225 (87 FS, 14 FA at 3 y)	FS or FA at 3 y	3–6 mo	↓	*Citrobacter*		
					↓	***Clostridium***		
					↓	*Dialister*		
					↓	*Dorea*		
					↓	*Haemophilus*		
					↓	*Lactococcus*		
					↓	*Oscillospira*		
2018	Stokholm[87]	690 (60 asthma at 5 y)	Asthma at 5 y	1 w, 1 mo, 1 y	↓	***Alistipes***		
					↓	*Bifidobacterium*		
					↓	*Dialister*		
					↓	***Faecalibacterium***		
					↓	*Flavonifractor*		
					↓	***Roseburia***		
					↓	***Ruminococcus***		
					↑	*Veillonella*		
2017	Tanaka[121]	56 (27 allergic disease at 3 y)	Any allergic disease at 3 y	1, 2, 6, 12 mo	↓	*Leuconostoc*		
					↓	*Veillonella*		
					↓	*Weissella*		
					↑	***Clostridium***		
					↑		Enterobacteriaceae	
2016	Bunyavanich[122]	226 (128 resolved milk allergy by 8 y)	Milk allergy resolution at 8 y	3–16 mo	↓			Clostridia
					↓			Firmicutes
2016	Chen[83]	45 (23 FS)	FS at 6–12 mo	6–12 mo	↓			Bacteroidetes
					↑			Firmicutes
					↑		Bacteroidaceae	
					↑		Clostridiaceae	
					↑		Ruminococcaceae	
2016	Fujimura[84]	130 (32 AD at 2 y, 17 asthma at 4 y)	AD at 2 y or asthma at 4 y	15–138 d	↓	*Akkermansia*		
					↓	*Bifidobacterium*		
					↓	***Faecalibacterium***		
					↑	*Rhodotorula*		

↑ represents an increase in patients with allergic diseases and ↓ represents a decrease in patients with allergic diseases. Butyric acid-producing bacteria (BAPB) at the genus level are shown in bold. The proportion of BAPB in the gut microbiota was reported to be lower in four of six studies.
AD, atopic dermatitis; FA, food allergy; FS, food sensitization; y, year(s); mo, month(s); w, week(s); d, day(s).

Mechanistic link between dysbiosis and allergic diseases: Tregs and butyric acid-producing bacteria

Tregs are roughly grouped into those expressing Helios and Neuropilin-1 that became differentiated in the thymus (thymus-derived Tregs, tTregs) and those that do not express Helios or Neuropilin-1 that differentiated from naïve T cells in peripheral tissue (peripherally induced Tregs, pTregs). BABP (e.g., some *Clostridium* species,[77] Lachnospiraceae, and *Faecalibacterium* belonging to Ruminococcaceae) produce butyric acid in the colon. Butyric acid induces the differentiation of naïve T cells into pTregs in the colon.[48]

As an inhibitor of histone deacetylase, butyric acid promotes histone acetylation in the *Foxp3* gene promoter region as well as in the intragenic enhancer region (i.e. conserved noncoding sequence 3) in naïve T cells and consequently increases the expression of Foxp3, the master transcription factor of Tregs. In addition, dendritic cells produce retinoic acid when exposed to butyric acid, which induces Tregs via the activation of GPR109A and consequently contribute to the induction of Tregs.[91] Induced pTregs play an important role in maintaining the homeostasis of biological defense responses, producing immunosuppressive cytokines such as interleukin 10 (IL-10) or transforming growth factor-beta (TGF-β) that downregulate excessive immune

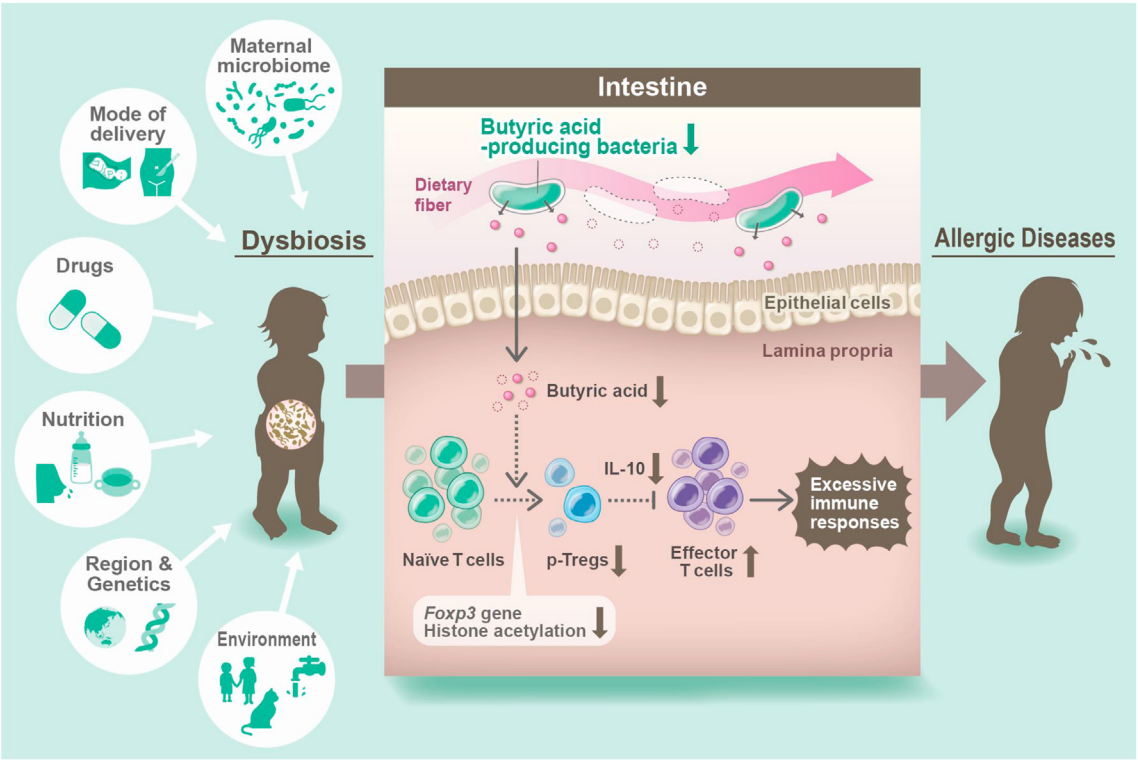

Fig. 1. Hypothesized relationship between dysbiosis characterized by fewer BAPB and the onset of allergic diseases. Due to dysbiosis arising from various factors including cesarean delivery and antibiotic use, which is characterized by fewer BAPB, the concentration of intestinal butyric acid concentration decreases. This decrease in butyric acid concentrations leads to the suppression of naïve T cells differentiating into Tregs, which impairs the ability of the immune system to suppress excessive immune responses, resulting in the onset of allergic diseases.

responses by effector T cells such as Th1 and Th17 cells. In addition, cytotoxic T lymphocyte–associated antigen-4 (CTLA-4, also known as CD152) expressed in Tregs acts as an immunosuppressor by binding to ligands such as CD 80/86 on antigen presenting cells.[92] In an animal study, the excessive immune response in *Foxp3* mutant mice was suppressed by the introduction of $CD4^{+}CD25^{+}$ T cells derived from wild-type mice,[93] suggesting that Tregs play an important role in the regulation of allergic responses.

Mechanistic link between dysbiosis and allergic diseases: BAPB in the gut microbiota of patients with egg allergy

We conducted a study to determine whether children with chicken egg allergy have dysbiosis characterized by fewer BAPB.[6] Stool samples were collected from 18 children with egg allergy with a median age of 3.1 years (interquartile range [IQR], 1.5–5.5), and 22 healthy controls, with a median age of 4.0 years (IQR,

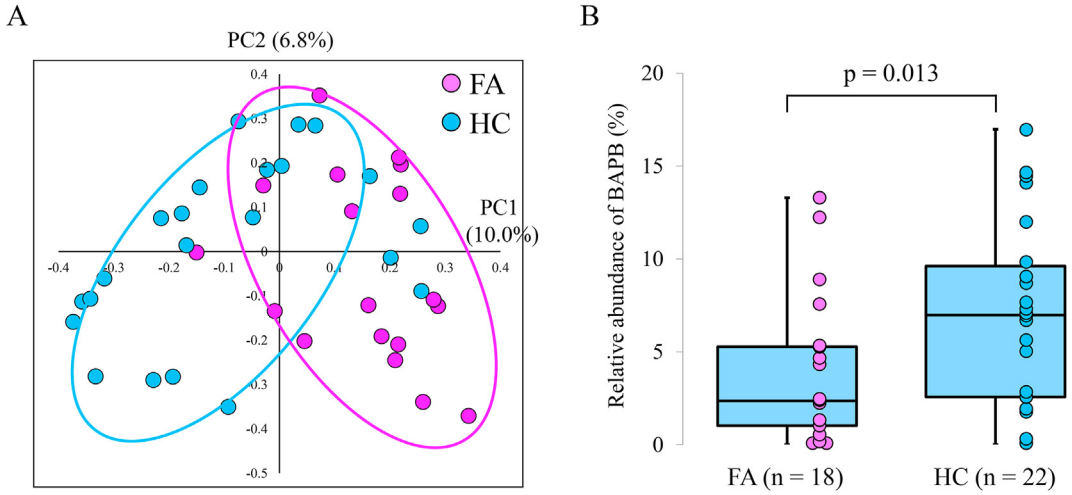

Fig. 2. Beta diversity **(A)** and proportion of BAPB **(B)** in children with egg allergy compared with healthy controls. **(A)** Principal coordinate (PC) analysis plots of Bray–Curtis dissimilarity were created for both groups. Pink and blue dots represent samples from the FA and HC groups, respectively. Clustering distances reveal the distinct structure of the gut microbiota in the two groups. **(B)** The relative abundance of BAPB was significantly lower in the FA group ($p = 0.013$). FA, food allergy; HC, healthy control; BAPB, butyric acid-producing bacteria. Modified from Reference 6 with permission by John Wiley and Sons.

2.9–6.1). Participants were diagnosed with egg allergy based on either a positive result to a physician-supervised oral food challenge to egg or a convincing reaction and sensitization to egg with an egg-specific immunoglobulin E level >0.35 kUA/L. The proportion of BAPB, alpha diversity, and beta diversity were assessed using 16S rRNA sequencing. The allergy group had lower alpha diversity. Beta diversity analysis showed distinct clusters in the allergy and healthy control groups (Fig. 2A). It is noteworthy that the proportion of BAPB was significantly lower in the allergy group (2.3% [1.0–5.2] vs. 6.9% [2.5–9.6]; $p = 0.013$) (Fig. 2B). The median percentage of Tregs in the allergy group was 2.7%, which was lower than the normal reference range. From this study, we revealed that children with egg allergy have a distinct gut microbiota that is characterized by fewer BAPB and a lower proportion of Tregs among peripheral lymphocytes.

Preventative and therapeutic interventions targeting the gut microbiota

Following the deeper understanding of the gut microbiota's role in various diseases and in health, approaches to restore and maintain the favorable balance of the gut microbiota are actively being studied. Current available approaches include probiotics, prebiotics, synbiotics, postbiotics, and fecal microbiota transplantation (FMT). Probiotics are defined as live microorganisms administered in appropriate amounts, which have a positive effect on host health according to the 2002 World Health Organization report. Bacteria of the genera *Lactobacillus, Bifidobacterium*, and *Streptococcus* are most commonly used. Prebiotics are defined as non-digestible dietary substances that benefit the host by promoting the growth of beneficial intestinal microorganisms. Prebiotics include oligosaccharides, dietary fiber, and other non-digestible carbohydrates.[94] Synbiotics are a combination of prebiotics and probiotics, synergistically promoting gastrointestinal health by improving survival and providing live microbial dietary supplements.[95] Postbiotics are substances produced or released by the metabolic activity of microorganisms that benefit the host directly or indirectly.[90] FMT is a procedure that delivers donor stool to the intestinal tract of a recipient to change the recipient's gut microbial composition in a beneficial manner.

Therapeutic interventions for IBD targeting the gut microbiota

The two major IBDs, ulcerative colitis (UC) and Crohn's disease (CD), is related to dysbiosis.[96,97] This relationship has led to the advancement of treatments targeting dysbiosis. In this section, current evidence on treatment targeting dysbiosis in IBD based on meta-analyses will be discussed. Many studies using probiotics have been conducted; most of them involve *Bifidobacterium* and *Lactobacillus*. In a 2020 Cochrane review, although the evidence level is low, the effectiveness of probiotics versus placebo was shown based on remission rates in patients with UC.[98] On the other hand, the meta-analysis did not draw any conclusions regarding the role of probiotics in remission maintenance for UC because of the small number of randomized controlled trials (RCTs) and conflicting results between studies.[99] In patients with CD, the expectations of probiotics to prevent relapse is higher because surgical treatment is not a feasible option. However, a meta-analysis that included three RCTs did not report that probiotics (*Lactobacillus*) are effective in preventing endoscopic relapse.[100] Currently, the European Society for Clinical Nutrition and Metabolism recommends specific probiotics for active UC.[101] However, the American Gastroenterological Association does not recommend probiotics for either UC or CD.[102]

FMT has gained attention as a feasible treatment option for dysbiosis. A 2018 Cochrane review with results of a meta-analysis that analyzed four RCTs concluded that the FMT group had significantly higher remission rates than controls.[103] However, adverse events like *Clostridium difficile* infection have been observed after FMT. Thus, FMT needs to be conducted carefully in recognition that it is a high-risk treatment. FMT is not yet a standardized treatment option for UC because the ideal number of treatments and ideal administration method have not been established. In the same review, a meta-analysis was not conducted for CD because there were not enough RCTs. In another meta-analysis of FMT for CD, effectiveness was not demonstrated.[104]

There are few studies about prebiotics and postbiotics. Casellas *et al.* reported that oligofructose-enriched inulin reduces intestinal inflammation in patients with UC.[105] In addition, Kanauchi *et al.* have conducted a clinical trial using germinated barley. They reported that it had a prebiotic effect, with reductions in clinical activity index, and that it was effective as maintenance therapy in patients with UC.[106]

Regarding postbiotics, among metabolites produced by the gut microbiota, bile acids, SCFAs, and tryptophan metabolites are related to the pathology of IBD.[107,108] A study of enemas containing SCFAs showed no positive clinical outcomes.[109] The results of a trial of oral tryptophan metabolites in patients with IBD are awaited.[110]

Taken together, following the increase in the number of RCTs, meta-analyses have shown the efficacy of probiotics and FMT in UC but not in CD. Prebiotics and postbiotics need further investigation before becoming treatment options.

Interventions targeting the gut microbiota in allergic diseases

In this section, we will introduce clinical interventions by allergic disease type. Although many interventions have been conducted to prevent or treat allergic diseases, several meta-analyses have not reached any conclusions with high-quality evidence showing that correcting the gut microbiota can prevent or treat allergic diseases.[111–113] Although many studies use probiotics as an intervention, difficulties optimizing factors such as probiotic type, dose, and duration of administration might make it difficult for such studies to reach a conclusion with high-quality data.

To prevent food allergy in infants and toddlers, the efficacy of probiotics given to pregnant mothers or infants was analyzed in a meta-analysis. It concluded that neither was beneficial.[113] The probiotics used mainly contained the genus *Lactobacillus* or *Bifidobacterium*, usually at a dose of 10^9–10^{10} colony forming units (CFUs)/day.

In atopic dermatitis, the effect of probiotics on eczema was analyzed in a meta-analysis in a Cochrane review.[113,114] The analysis included 13 placebo-controlled trials. Most used 10^9 CFU/day of the genus *Lactobacillus* as the intervention. The meta-analysis did not reach the conclusion that probiotics has clinical benefits on eczema.

In bronchial asthma, a meta-analysis of the effects of probiotics on pregnant mothers and infants showed that they did not have a significant effect in preventing the onset of asthma.[111] The outcomes of wheezing and lower respiratory tract infection during childhood were not affected. Most studies used the genus *Lactobacillus*, at a dose of 10^9–2.4×10^{10} CFU/day.

In allergic rhinitis, no meta-analyses of the effects of probiotics on the management of allergic rhinitis have been reported. However, Fassio *et al.* reviewed 10 studies on probiotics for patients with allergic rhinitis, of which five studies reported significant decreases in symptom score and improved quality of life, suggesting that probiotics have a beneficial effect.[115] The genera *Bifidobacterium* and *Lactobacillus* might be efficient for treating allergic rhinitis, which warrants further investigation.

Strategies focusing on butyric acid-producing bacteria to prevent and treat allergic diseases

Although it is not yet proven, if decreases in intestinal levels of BAPB and butyrate are related to the onset of allergic diseases by reducing the number of Tregs, clinical strategies could include increasing BAPB levels using prebiotics or probiotics, increasing butyrate levels using postbiotics, or both. In this section, we will discuss whether each strategy is feasible. First, as mentioned above, probiotics are unlikely to be effective for treating allergic diseases. Although there is room for future investigations of probiotic treatments using BAPB, the load of bacteria contained in probiotics taken orally is generally small compared to the amount of bacteria comprising the gut microbiota, which makes it difficult for the bacteria in the probiotics to stably reside in the colon.[116] Therefore, probiotics targeting the gut microbiota may not be the ideal strategy for treating and preventing allergic diseases.

Considering prebiotics, BAPB produce butyrate by digesting fibers. We have reported that prebiotics rich in fiber increase BAPB levels.[117] In a study where 18 healthy adults received 40 g of granola containing 20.4 g of functional barley (BARLEY max®) once daily for 4 weeks, BARLEY max® acted as a prebiotic with twice the fiber and four times the amount of resistant starch found in regular barley. We compared the proportion of BAPB and concentration of butyrate in feces. As a result, the median proportion of BAPB in the gut microbiota increased from 5.9% to 8.2% and the concentration of butyrate in the feces increased from 0.99 mg/g to 1.43 mg/g.[117] We are expecting future clinical applications of this barley as an efficient prebiotic to prevent the development of allergic diseases.

We would also like to discuss butyrate as a postbiotic. Butyrate induces naive T cells to differentiate into Tregs in vivo and in vitro.[48] However, SCFAs, including butyrate, cannot reach the colon since they are absorbed in the stomach or duodenum,[118,119] which means that oral intake of butyrate does not elevate butyrate concentrations in the colon. To overcome this challenge, oral administration of chemically modified acetylated butyric starch and enemas containing butyrate was used to elevate butyrate concentrations in the colon, resulting in higher Treg levels in the colon.[118,120] Although it has not been reported, butyrate capsules that dissolve in the colon might be another efficient strategy.

In summary, we are expecting prebiotics and postbiotics containing butyrate to be more effective for inducing Tregs than probiotics. Prebiotics might be more feasible than postbiotics because prebiotics are safer and easier to access as they are mainly food.

FMT is another option to drastically change the gut microbiota. However, no evidence is available to recommend FMT as a preventative or therapeutic option given the risk of severe infections.

Future studies are warranted using not only probiotics but also prebiotics and postbiotics to alter the gut microbiota, hopefully leading to the prevention and treatment of allergic diseases.

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Conflict of interest

The authors have no conflict of interest to declare.

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