Invited review article

Development of the gut microbiota in infancy and its impact on health in later life

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abstract

Gut microbial ecology and function are dynamic in infancy, but are stabilized in childhood. The ‘new friends’ have a great impact on the development of the digestive tract and host immune system. In the first year of life, especially, the gut microbiota dramatically changes through interactions with the developing immune system in the gut. The process of establishing the gut microbiota is affected by various environmental factors, with the potential to be a main determinant of life-long health. In this review, we summarize recent findings regarding gut microbiota establishment, including the importance of various factors related to the development of the immune system and allergic diseases later in life.

Introduction

Several hundred bacterial species and a total of $10^{14}$ cells colonize the human gastrointestinal (GI) tract in a mutualistic relationship with the host and its immune system. A healthy gut microbiota is stable and serves various useful functions such as metabolizing barely digestible polysaccharides, detoxifying toxic products, serving as a barrier against pathogens, and aiding in the development of the host immune system. However, it has become clear through recent studies that dysbiosis, in which the symbiotic relationship between the host and gut microbiota is altered, is associated with various diseases, including inflammatory bowel disease (IBD), irritable bowel syndrome, obesity, allergy, autoimmune disease, and brain disorders.

Although intestinal bacterial colonization begins when a fetus is in the lower uterus, an infant’s gut microbiota is established after birth. The establishment of a stable gut microbiota generally accompanies two big transitions in infancy. The first transition occurs soon after birth, during lactation, and results in dominance of the gut microbiota by *Bifidobacterium*. The second transition occurs during the weaning period, with the introduction of solid foods and continuation of breast milk feeding, and results in the establishment of an adult-type complex microbiome dominated by the phyla *Bacteroidetes* and *Firmicutes*. These alterations continue until three years of age and, subsequently, humans acquire stable gut microbiota maintained in well-balanced host-microbiota symbiotic states called “Enterotypes”. Enterotypes are classified into three types that are dominated by *Bacteroides*, *Prevotella*, and other *Firmicutes*. The early establishment of gut microbiota is affected

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by several factors such as delivery mode (cesarean delivery vs. vaginal delivery), breast milk vs. formula feeding, antibiotic usage, and timing of the introduction of solid foods and cessation of milk feeding.\textsuperscript{24} In addition, intestinal bacterial colonization has profound effects on the development and physiology of the host immune system in early life and affects health and disease in later life. In particular, colonization with intestinal bacteria is necessary for normal immune system development, as indicated by the loss of immune function in germ-free mice.\textsuperscript{25–27} A number of previous studies have shown that intestinal bacteria and their metabolites, including short chain fatty acids (SCFA), play an important role in the proliferation and differentiation of T cells, such as regulatory T (Treg) and helper T (Th) cells, and B cells such as immune globulin (Ig) A- or IgG-secreting B cells.\textsuperscript{28}

Therefore, development of the gut microbiota in infancy occurs during a ‘critical window,’ and a disturbance in this process may cause immune diseases such as food allergies, atopic dermatitis, and asthma.\textsuperscript{29} To elucidate this association, a large number of studies on microorganisms and microbial ecology, as well as work in animal models and epidemiological surveys, have been conducted. The recent increase in access to next-generation sequencers has allowed researchers to gain deep insight into intestinal ecosystems at the molecular level. On the other hand, hygiene hypothesis has been introduced into gut microbiology to correlate changes in life style with marked increase in childhood allergy in the past half century. This review aims to provide an overview of the recent advances in research on infant gut microorganisms and health and disease, including childhood allergies.

**GI tract microorganisms in utero**

The GI tract has traditionally been considered sterile until it is colonized by microorganisms residing in the environment at birth. However, recent studies have revealed the presence of microorganisms in amniotic fluid,\textsuperscript{30–32} fetal membranes,\textsuperscript{33} umbilical cords, placenta,\textsuperscript{34} and meconium.\textsuperscript{35–37} Gosalbes et al.\textsuperscript{37} showed that meconium microorganisms could be classified into two types: the first is less diverse and dominated by bacteria in the family Enterobacteriaceae, and the other is more diverse and dominated by bacteria in the phylum Firmicutes, especially lactic acid bacteria. These microbial communities differ from the microorganisms of the vagina, feces, or skin of a pregnant women, but resemble the microbiota of the amniotic fluid, suggesting that microbes in the meconium originate from the uterus of the mother. A fetus’s GI tract appeared to be colonized by bacteria through amniotic fluid that was swallowed. Further, the type of microbe in the meconium was associated with maternal factors such as history of allergies and could have consequences for childhood health.

Experimental work with mice has demonstrated efflux of bacteria from a mother’s gut to that of her fetus.\textsuperscript{38} Pregnant mice were orally inoculated with a genetically labeled *Enterococcus faecium* strain that was previously isolated from the breast milk of a healthy woman. The strain was detected in the amniotic fluid of the inoculated animals. This suggests that bacteria might be transferred from the oral cavity to the uterus, possibly via the blood stream. Oral bacteria are known to reach the uterus via the blood stream, particularly in periodontal disease.\textsuperscript{39} This route is also supported by the findings of Aagaard et al.\textsuperscript{40} and others, which has shown that the genetic and taxonomic composition of the placental microbiota closely resemble those of the oral cavity.

### Compositional and functional development of the gut microbiota during infancy (Fig. 1)

After birth, the gut microbiota of a newborn is transiently dominated by *Enterobacteriaceae* and *Staphylococcus*.\textsuperscript{41} Thereafter, an infant’s gut microbiota is dominated by *Bifidobacterium* and some lactic acid bacteria.\textsuperscript{42} *Bifidobacterium*-dominated microbiota, called “Bifidus flora,” is maintained until the introduction of solid food.\textsuperscript{41,42} After weaning, *Bifidus flora* is outcompeted by adult-type microorganisms, represented mainly by bacteria in the genera *Bacteroides*, *Prevotella*, *Ruminococcus*, *Clostridium*, and *Veillonella*, which colonize an infant’s intestines.\textsuperscript{41} Eventually, by about three years of age, a typical adult-like gut microbiota is established.\textsuperscript{22} The functions of the gut microbiota also change greatly before and after the introduction of weaning foods. The functional repertoire of an infant’s microbiota changes during the first year of life, as the early microbiota before weaning is enriched in bacteria with genes that

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**Fig. 1.** Fetal-to-childhood gut microbiota colonization and important factors affecting this process. Establishment of the gut microbiota may begin in utero and be affected by dynamic shifts in early life. Diversity of the gut microbiota increases with age until it becomes a stable adult microbiota. This process of establishing the gut microbiota is affected by various factors such as delivery mode, methods of milk feeding, the introduction of solid foods, and foods consumed daily in childhood.
facilitate lactate utilization, whereas, after weaning, solid foods promote the growth of bacteria enriched in genes coding to allow the utilization of a larger variety of carbohydrates, vitamin synthesis, and xenobiotic degradation.22,41,43

Effect of the mode of newborn delivery

A number of studies have indicated that the mode of delivery affects the development of the gut microbiota in early life. Interestingly, the gut microbiota of a newborn will closely resemble the microbiota that it encountered during birth. In vaginally delivery infants, gut microorganisms resemble their mothers’ vaginal microbiota, which are dominated by Lactobacillus, Prevotella, or Staphylococcus, whereas the microbiota of infants born by caesarean section are most similar to skin microbiota, which is dominated by Staphylococcus, Corynebacterium, and Propionibacterium.50 In addition, some studies have shown that colonization by Bacteroides and Bifidobacterium is delayed for one month after birth, whereas Clostridium difficile was abundant at one month.44,45 Underrepresentation of Bacteroides was also observed in the microorganisms of infants born by caesarean section for three to four months after birth. In addition, the same studies have shown that infants born by elective caesarean section had particularly low bacterial diversity.46 Caesarean birth has been associated with an increased risk for immune disorders such as allergic rhinitis, asthma, and celiac disease,47–49 as described in detail below.

Beneficial factors in breast milk

Infant feeding methods, namely breast milk feeding and formula feeding, greatly affect the development of the gut microbiota in early life. Human milk contains proteins, fats, and carbohydrates, as well as immunoglobulins and endocannabinoids. The oligosaccharides in human milk (HMO) such as galactooligosaccharide (GOS), are one of the main components of breast milk. They are only partially digested in the small intestine and mostly reach the colon, where they are fermented, mainly by Bifidobacterium, to produce short-chain fatty acids.48,56 Sakurama et al. reported that bifidobacterium spp. have an enzyme named lacto-N-biosidase to facilitate assimilation of GOS.53 Matsuki et al. reported that, as the number of bifidobacterium increased, the amount of HMOs in feces decreased, and the amount of acetic acid and lactic acid increased in infants at one month of life. Therefore, HMOs have a clear probiotic effect by selectively stimulating the development of a Bifidobacterium-rich microbiota.40

Recently, milk formula has been improved, notably by the inclusion of some oligosaccharides, which makes it possible for an infant to establish a Bifidobacterium-rich microbiota.54 However, compared with breastfed infants, formula-fed infants still have distinct features of their microbiota, such as the overrepresentation of C. difficile.55 Another study indicated that the microbiotas of formula-fed infants are enriched with anaerobic organisms such as Bacteroides and Clostridium, whereas those of breastfed infants are more commonly colonized by aerobic organisms.53,54 A recent study reported that supplementation with pasteurized donor human milk was partially successful in promoting a microbial community similar to that of breastfed infants and in promoting rapid increases in bacterial diversity.55

Breast milk contains numerous factors that modulate and promote the development of the immune system in infancy, including immunoglobulins such as IgA and IgG, antimicrobial compounds such as lysozyme and lactoferrin, immune regulatory cytokines such as TGF-β and interleukin 10 (IL-10), and lymphocytes that express gut homing markers.56–58 These substances in breast milk select bacteria that colonize the GI tract. For example, immune regulatory cytokines such as IL-10 and TGF-β in breast milk facilitate tolerance of the host immune system to intestinal bacteria and promote infant IL-10 production.59,60

Bifidobacterium, whose growth is promoted by HMOs, and especially Bifidobacterium infantis, has been reported to directly correlate with the amount of secreted IgA and to have anti-inflammatory effects.61,62 Recent studies have shown that breast milk is not sterile. It contains as many as 600 different bacterial species and 10⁷–10⁹ cfu/mL of bacteria cells.63 Genera of bacteria isolated from breast milk include mostly lactic acid bacteria such as Lactobacillus, Leuconostoc, Streptococcus, Enterococcus, Lactococcus, and Weissella, as well as some beneficial Bifidobacterium species.64–66 In addition, studies using molecular approaches indicate that gram-negative bacteria are also present, including Serratia, Pseudomonas, and some typical inhabitants of the oral cavity such as Veillonella, Leptotrichia, and Prevotella.67 This suggests that some bacteria may be transferred from mother to child via breast milk.

Fatty acids (FA) in breast milk are also associated with host health and development of the immune system. TGF-β levels in breast milk have been reported to correlate positively with polyunsaturated FA content.68 Some cohort studies have shown that the ratio of polyunsaturated FA to saturated FA is related to an infant’s risk of atopic dermatitis.69,70 In addition, the microbiotas and FA profiles in milk were different in Europe (Spain and Finland), Africa (South Africa), and Asia (China).71 However, there is little understanding of the mechanisms underlying the effects of FA in breast milk on the development of the host immune system, and how they may be related to the establishment of the gut microbiota in infancy.

Perturbation by antibiotics

The use of antibiotic in early life has profound effects on the development of the gut microbiota. The use of antibiotics in infants shifts the composition of the gut microbiota toward a high abundance of Proteobacteria and low abundance of Actinobacteria populations.71,72 decreases the overall diversity of the infant’s microbiota, and selects for drug-resistant bacteria.73,74 According to some epidemiological surveys, the use of antibiotics in early life increases the risk of developing allergic diseases such as asthma, atopic disease, eczema, and type 1 diabetes.75

Tanaka et al.69 carefully examined the effects of antibiotic exposure in the early postnatal period on the development of the intestinal microbiota. The fecal microbiota of newborns orally administered a broad-spectrum antibiotic for the first four days of life were analyzed for two months. In the first week of the infants’ lives, the antibiotic-administered subjects showed less diversity in their fecal bacterial communities, with the attenuation of some bacterial groups, especially Bifidobacterium, as well as unusual colonization with Enterococcus. At one month of age, overgrowth of Enterobacteriaceae and Enterococcus was observed in infants in the antibiotic-treated group. Interestingly, caesarean-delivered subjects whose mothers were intravenously administered a closely related antibiotic in the same period showed similar, although weaker, associations with microbiota development. These results indicate that antibiotic exposure at the beginning of life greatly affects the development of neonatal intestinal microbiota.

Introduction of solid food

A large shift in the gut microbial community from Bifidobacterium-dominant to Bacteroidetes- and Firmicutes-dominant accompanies the introduction of solid foods, including indigestible carbohydrates, into an infant’s diet, although the specific taxa present before and after this point varies.41,42,76 At approximately
three years of age, bacterial composition and diversity is most like those of adults. These microbiotas remain fairly stable throughout adulthood in the absence of perturbations such as long-term dietary changes, disease-associated dysbiosis, or the use of antibiotics.

Recent metagenomics studies have offered in-depth insights into the functions of infant gut microbiotas. The infant gut rapidly acquires a functional gene pool dominated by carbohydrate metabolism genes, which is broadly similar to that of an adult. However, the functional repertoires of the infant microbiotas shift dramatically during the first year of life, as the earliest microbiotas are enriched in bacteria with genes that facilitate lactate utilization, whereas solid foods enrich microbiotas with bacteria with genes that code for the utilization of a larger variety of carbohydrates, vitamin biosynthesis, and xenobiotic degradation.

**Childhood microbiotas**

The gut microbiomes of children, compared with those of infants, show less variability among individuals and are more stable. Gut microbiotas in childhood are affected by geography and food culture. Nakayama et al. taxonomically assigned the gut microbiotas of 303 children from five Asian countries, namely Japan, China, Taiwan, Indonesia, and Thailand, and found that they clustered into *Bacteroides*-Bifidobacterium-dominant microbiotas (BB-type) and *Prevotella*-dominated microbiotas (P-type). The BB-type was most common in Eastern Asian, whereas the P-type was predominant in central Asia and South East Asia, with Indonesia having the highest abundance of P-type microbiotas. The establishment of two distinct intestinal microbial communities may be largely influenced by foods consumed daily, as shown by the P-type that is established in vegetarians.

The two types of microbiotas have been reported in many other cohort studies. Yatsunenko et al. characterized bacterial species in fecal samples from 531 individuals comprising healthy children and adults from the Amazonas of Venezuela, rural Malawi, and metropolitan USA. The gut microbiota of people from the USA were dominated by Bacteroides, whereas those of rural Venezuela and Malawi people were dominated by *Prevotella*. Lin et al. compared microbiotas of children in the USA and Bangladesh and found that Bangladeshi children had high bacterial diversity, with communities dominated by *Prevotella*, whereas US children had low bacterial diversity, with communities dominated by *Bacteroides* and *Firmicutes*. These results suggested that gut microbiotas of children in advanced countries are dominated by *Bacteroides* and *Firmicutes*, whereas those of developing countries are dominated by *Prevotella*. Further, these two microbiota-types are often observed within the same country, but are associated with level of development in an area. Nakayama et al. recently found that P- and BB-type microbiotas were represented in children living in rural and urban sites, respectively, on Leyte island in the Philippines, and that a type shift was associated with modernization of consumed foods, and notably a change to high-fat diets. The two sites sampled, namely Baybay and Ormoc, were only 50 km apart, and the children studied were mostly Filipino, suggesting that diet had a greater influence on gut microbial communities than host genetics. Indeed, the functional repertoires of the microbiotas of children on Leyte reflected dietary habits, and the microbiotas were enriched in bacteria with genes encoding bile acids that aid in lipid absorption or oligosaccharide-degrading enzymes involved in plant digestion in BB-type and P-type children, respectively.

It is notable that gut microbiotas differ between advanced and developing countries and between urban and rural areas, and that the occurrence of autoimmune diseases such as allergic diseases or IBD has coincided with industrialization in the past half century. Many papers have suggested the association of gut microbiota alterations with the development of allergies, which is expressed in the gut microbiota-mediated hygiene hypothesis.

**Interactions between gut microbiotas and host immunity**

Development of gut microbiotas between infancy and weaning is associated with immune system development. In particular, bacterial colonization is indispensable for the normal development of immunity, as indicated by the loss of immune function in germ-free mice. Furthermore, bidirectional communications have been proposed, in which intestinal bacteria affect not only the development of the immune system but also the host immune system influences the development of the gut microbiota. Immune factors in infancy, such as the presence of maternal antibodies and intestinal gut microbiota-primed B cell trafficking, play important roles in the selection of intestinal bacteria.

Through the placenta and breast milk, maternal antibodies such as IgG and IgA are introduced into infants. The presence of IgAs specific for intestinal bacteria are associated with differences in bacteria habitats in GI tracts. Bunker et al. showed that intestinal bacteria in the small intestine are bound to bacteria-specific IgA, whereas, in the large intestine, most bacteria are not bound to IgA. This result suggests that bacteria bound by IgA effectively colonize the small intestine. Furthermore, segmented filamentous bacteria (SFB) over colonize the GI tracts of IgA-knockout mice and strongly induce immunity. SFB play a role in shaping immune functions, such as promoting IgA secretion and promoting the development of intestinal cell lymphocytes and Th17 cells. Based on these findings, it is hypothesized that the interaction between bacteria and IgA plays important roles in the development of the immune system. Therefore, the establishment of gut microbiotas in early life can significantly influence the development of the immune system.
on these functions of IgA molecules, maternal IgA in breast milk functions similarly; thus, IgA may be involved in the selection of bacteria that colonize GI tracts in infancy.

Bacterial colonization of the gut also impacts differentiation of naïve T cells into Forkhead box P3 (FoxP3) Treg cells or various types of Th cells such as Th1, Th2, and Th17. Treg cells suppress the differentiation of naïve T cells into Th cells and have various anti-inflammatory effects, including suppression of the inflammatory activities of mast cells, basophils, and eosinophils, suppression of IgE, and induction of IgG. A number of intestinal bacteria, including Lactobacillus, Bifidobacterium, Bacteroides, Clostridium, and Streptococcus, as well as bacterial metabolites such as butyric acid and propionic acid, have been shown to induce Treg cells in various mouse models or cell culture. Treg cells are generated in the thymus (tTreg) and periphery (pTreg), and pTregs, but not tTregs, control mucosal Th2 inflammation in the gut and lungs. Recent studies have shown that pTregs are produced by intestinal bacteria and a symbiosis factor (polysaccharide A) produced by Bacteroides fragilis. On the other hand, each type of Th cell plays a distinct and key role in shaping and amplifying the immune response by producing cytokines that can suppress other types of Th cells. Th17 cells, which are abundant in the mucosa, secrete cytokines, including IL-17, IL-17F, and IL-22. These cytokines improve the barrier function of the GI tract and protect against pathogen and fungi. Th17 cells are promoted by bacterial flagella, unmethylated DNA, and adenosine triphosphate (ATP). Mutual regulation of Th1 and Th2 cells is considered a critical factor for immune homeostasis. Indeed, excessive Th1 or Th2 activation results in chronic inflammation and autoimmunity or allergic disease.

**Gut microbiota aberrations associated with allergy development**

Colonization of intestines with bacteria and the development of a gut microbiota in infancy are closely related to the development of the immune system. In fact, altered development of gut microbiotas is suspected to be associated with the onset of autoimmune or allergic diseases.

Numerous cohort studies have shown that alterations in the gut microbiota during infancy and early childhood are associated with allergic diseases (Table 1). Atopic eczema/dermatitis reflects inflammation of the skin and is the result of a process called atopic march, which constitutes a strong risk factor for the development of other allergic disease. Some cohort studies have shown that infants with atopic dermatitis have a low level of bacterial diversity in early infancy, as well as a low abundance of Bifidobacterium and Bacteroides and high abundance of Enterobacteriaceae. Fuji-mura et al. reported that infants with high relative risk of atopic dermatism and asthma showed lower relative abundances of certain bacteria such as Bifidobacterium, Akkermansia, and Faecalibacterium, high relative abundances of particular fungi such as Candida and Rhodotorula, and distinct fecal metabolomes enriched with pro-inflammatory metabolites, 12, 13-DiHOME.

Food allergies are a disease with symptoms such as inflammation of the skin and GI tract resulting from specific food intake. Symptoms, in most cases, appear when solid foods are introduced in association with weaning. Food allergies in infancy are thought to impair oral tolerance. Establishment of oral tolerance is a crucial event mediated by bacterial colonization in infancy, and it is required for normal function of the digestive tract after weaning.

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**Table 1**

<table>
<thead>
<tr>
<th>Surveyed country</th>
<th>Allergic disease</th>
<th>Age</th>
<th>No.</th>
<th>Features of gut microbial community or metabolites</th>
<th>Ref.</th>
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<tr>
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<td>Atopic dermatitis</td>
<td>y2</td>
<td>44</td>
<td>Enterococcus</td>
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<td>Lactation</td>
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<td>29</td>
<td>Clostridium</td>
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<td>Bacteroides</td>
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<td>y2</td>
<td>12</td>
<td>Bacteroides</td>
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<td>Food allergies</td>
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<td>139 (y1)</td>
<td>Acinetobacter</td>
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<tr>
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<td>w1, m1, m2</td>
<td>22</td>
<td>Bacteroides</td>
<td></td>
</tr>
<tr>
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<td>Food allergies</td>
<td>w1, m1, y1</td>
<td>40</td>
<td>Bacterial diversity</td>
<td></td>
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<td>Food allergies</td>
<td>m2–m11</td>
<td>79</td>
<td></td>
<td></td>
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<td>m3, y1</td>
<td>166</td>
<td>Bacterial Diversity</td>
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<td>m3, y1</td>
<td>319</td>
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<td>w1, m1, m2</td>
<td>117</td>
<td></td>
<td></td>
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</tbody>
</table>

1 y, year of age; m, month of age; w, weak of age; †, high abancance; ‡, low abundance.
2 The number in parentheses indicates the year of publication.
Ling et al. showed that infants with food allergies before one year of age have a specific gut microbiota showing lower relative abundances of *Bacteroides* and *Clostridium* XVIII and higher relative abundance of *Clostridium sensu stricto* and *Anaerobacter*. Azad et al. studied infants with food sensitivity at one year of life and found that they had low-diversity and *Enterobacteriaceae*-dominated microbiota at three months of age and showed higher abundances of *Bacteroides* at one year of age, relative to children without food sensitivities.

The authors of this review found that the gut microbiota of infants with food allergies during the first two years of life showed lower relative abundances of some lactic acid bacteria and *Veillonella* in the lactation period, and had low-diversity and *Enterobacteriaceae*-dominant microbiotas, with colonization by *Clostridium paraparaputricum* and *Clostridium tertium*. On the other hand, Bunyanuvanich et al. conducted a cohort study examining milk allergies and found that children who resolved milk allergies by the age of eight years had microbiotas with higher abundances of bacteria in the phylum *Firmicutes* and family *Clostridiaceae* during the lactation period, whereas the microbiota of children with persistent milk allergies showed higher abundances of *Bacteroides*.

**Gut microbiota-mediated hygiene hypothesis**

The number of people with allergies rose drastically in the past half century after world industrialization. This phenomenon is often explained by the “hygiene hypothesis,” which state that less exposure to parasites and microbes leads to an overreactive immune system. An imbalance between type 1 and type 2 Th cells can indeed interprets allergy crisis in advanced countries with modern hygiene environment that biases humoral immunity in human body. With the eradication of certain pathogens, less exposure to environmental and commensal microorganisms may contribute to the effects hypothesized. Indeed, the prevalence of allergic diseases was found to be significantly higher in urban children than in rural children, although the environment where the rural children were living also had a much higher level of bacterial endotoxin. Interestingly, *Acinetobacter Iwoffi* F78, isolated from a farming environment, showed a potent allergy-protection effect by inducing Th1 polarization in the respiratory system.

The hygiene hypothesis has been extended to intestinal microbiology. Bjorgsten et al. examined differences in gut microbial composition between allergic and non-allergic children, as well as between children living in a developed country, Sweden, and a developing country, Estonia. Following this study, a number of epidemiological studies have found differences in gut microbial composition between allergic and non-allergic children, even though the differences were not always consistent. The discrepancies may result from differences in races, genetics, diets, living environments, or other factors, in addition to study methodologies, including sampling ages or analytical methods used to investigate microbial composition. Our group has also addressed differences in gut microbiotas between one-month-old Japanese infants who later did and did not develop allergic diseases. Indeed, allergic infants were more commonly colonized by bacterial in the genus *Bacteroides* and less often colonized by bacteria in the genera *Acinetobacter* and *Clostridium*. It is interesting to find that Acinetobacter was a less frequent colonizer of allergic infants in Japan. Recently, Vatanen et al. followed gut microbiota development from birth until age three years in 222 infants in Northern Europe. Early-onset autoimmune diseases are common in Finland and Estonia, but are less prevalent in Russia. Interestingly, they found that *Bacteroides* species were not abundant in Russians, but dominate in Finnish and Estonian infants. This coincides with our previous finding that a high abundance of *Bacteroides* was associated with the development of allergies in Japanese infants. *Bacteroides* LPS is known to be structurally distinct from that of *Escherichia coli*, and it inhibits innate immune signaling and endotoxin tolerance, which is normally induced by commensal members of gram-negative bacteria such as *E. coli*. Early colonization by such immune-silencing microorganisms may have precluded aspects of immune education in allergic children in Finland and Estonia.

Childhood food allergies have emerged in a second wave of the allergy epidemic, following a first wave of asthma, atopic dermatitis, and allergic rhinitis that appeared in association with industrialization in the past half century. However, the cause of this second epidemic is yet to be identified. Recently, omics technology, especially metagenomics and metabolomics, has progressed dramatically, facilitating examinations of the structural and functional aspects of gut microbial communities, and advanced animal experiment technologies are now available that allow us to gain insight into the cellular and molecular mechanisms underlying the associations between gut microbiota and childhood allergies.

**Concluding remarks**

Stable microbial communities are established through dynamic changes in infancy and are affected by various environmental factors such as the mode of delivery and methods of milk feeding. Simultaneously, the immune system matures through bidirectional interactions, with the gut microbiota promoting the development of the immune system but also the host immune system shaping the development of the gut microbiota. Alterations in the development of gut microbiotas during infancy can have a variety of negative effects on immune health and the onset of allergies. Although our knowledge of these effects is far from complete, many studies are now allowing us to determine the causes and effects described in the gut microbiota-mediated hygiene hypothesis. These insights may help us develop a society with less allergy diseases than in the pre-industrialized era.

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**Conflict of interest**

The authors have no conflict of interest to declare.

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