J Gastroenterol (2015) 50:720–726
DOI 10.1007/s00535-015-1082-z

The Japanese Society of Gastroenterology

REVIEW

Gut microbiota and the development of pediatric diseases

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Received: 6 April 2015 / Accepted: 9 April 2015 / Published online: 28 April 2015

Abstract The human gut harbors a huge number of microbes, which are collectively named "microbiota." The dynamic composition of the human gut microbiota is determined by multiple factors, including mode of delivery, diet, environment, and antibiotics. A healthy gut microbiota is helpful to the host in many aspects, including providing nutrients, protection from pathogens, and maturation of immune responses. Dysbiosis plays important roles in various diseases in infancy and later life: necrotizing enterocolitis, inflammatory bowel disease, obesity, and atopic diseases are some examples. Studies of functional metagenomics by newly developed techniques, such as next-generation sequencing, will not only elucidate the molecular mechanisms underlying gut microbiota–host interactions but will also provide new possibilities for disease prevention and treatment.

Keywords Gut microbiota · Early infancy · Diseases · Children

Introduction

A huge number of highly diversified microbes live inside and on the human body. They are collectively named "microbiota." The microbes that inhabit the human body outnumber a human's somatic cells by an estimated tenfold [1]. The number of genes in this huge number of microbes (microbiome) may exceed the total number of human genes by a factor of about 100 [2]. Humans benefit from symbiosis with these nonpathogenic microbes in many aspects. These collective genomes of the microbiome even provide us with traits we have not evolved on our own [3]. Humans can therefore be regarded as superorganisms composed of human and microbial components [1].

Recent advances in various culture-independent molecular technologies and computational methods had made microbiome analysis possible and have led to a broader understanding of various aspects of the microbiome in humans. These include microbiota development and differences between healthy and diseased human bodies. Many diseases have been linked to an aberrant microbiota in the intestines (dysbiosis) or other parts of the body. The promotion of health or control of diseases by manipulating the human body microbiota seems to be more and more realistic. This review is aimed at highlighting recent studies in the relations between the gut microbiota and diseases, with a pediatric perspective.

Development of the gut microbiota

Neonates are born sterile, but many parts of their bodies are colonized by various microorganisms thereafter. The composition of the gut microbiota is dynamic, with drastic changes occur during infancy and childhood [4]. The temporal progression of the composition of the gut microbiota and how the composition influences human diseases are currently under intensive investigation.

The gut microbiota of infants is a direct result of food ingested by them. However, multiple factors, including host genetics, gestational age, modes of delivery, and medication, especially antibiotics, also profoundly affect the development of the gut microbiota in infants. The

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microbiota of the mother and other family members or even household pets might play some roles as well [5]. A cohort study involving more than 6000 children revealed increased odds of developing type 1 diabetes mellitus in children with indoor exposure to dogs [6], which affected the host gut microbiota and subsequently dysregulated the immunity and caused diabetes mellitus.

Diet

It is not surprising that the gut microbiota is related to milk ingested by babies. Many studies reported a relative richer abundance of *Bifidobacterium* and *Lactobacillus* in the gut microbiota of breast-fed infants than that of babies fed with infant formula [4, 7]. Some factors such as human milk oligosaccharides contained in the breast milk might assist the growth of *Bifidobacterium* [7]. On the other hand, formula-fed infants are more frequently colonized by *Clostridium* spp., including *Clostridium difficile* [8]. Studies have shown bacterial communities in germ-free mice are rapidly altered by the diet [9]. It was reported that the *Bacteroides* enterotype was associated with consumption of animal protein and saturated fat, whereas the *Prevotella* enterotype was associated with a carbohydrate-rich diet [10].

Delivery and gestation

The beginning of gut microbiota development can be traced back to delivery or even earlier. The microbiota of vaginally delivered newborns is different from that of babies delivered via cesarean delivery. The former have a microbiota representing the maternal vaginal and gut microbiota, whereas the latter exhibit a microbiota representative of the maternal skin microbiota and the environment, including *Staphylococcus* spp. [11]. *Lactobacillus*, *Prevotella*, *Escherichia*, *Bacterioides*, *Bifidobacterium*, and *Streptococcus* are the prominent genera found in the gastrointestinal tract of vaginally delivered babies [8]. Children born by cesarean delivery are initially exposed to non-maternally derived environmental microbes from equipment, clothes, bed sheets, nursing staffs, or other infants. The proportion of *Bifidobacterium* and *Bacteroides* spp. was reduced in infants delivered via cesarean delivery [8]. Microbial diversity is also low in infants delivered by cesarean delivery within the first 2 years of life [12]. Regardless of the delivery mode, bacterial communities among newborns exhibited a uniform site-specific distribution across different body parts as early as 1–3 months after birth [13]. Maternal impact on the gut microbiota of infants begins before delivery. Maternal factors such as antenatal infections, antibiotic use, smoking, and length of the gestation period (preterm or term) might affect colonization of the gut microbiota in infants [14].

Prematurity itself may also impact the composition of the gut microbiota. Premies inevitably need prolonged hospital stay. Hospitalization may lead to cross-transmission of bacterial flora among hospital staffs and other patients. Studies showed premature infants with a gestational age of less than 33 weeks exhibited significantly reduced bacterial diversity [15].

Antibiotics

Antibiotic treatment obviously leads to changes in the composition of the gut microbiota. Growth of otherwise dominant bacterial phyla in the human gut may be influenced significantly. Fouhy et al. [16] showed that infants exposed to ampicillin and gentamicin shortly after birth tend to harbor a higher abundance of *Proteobacteria*, *Actinobacteria*, and *Lactobacillus* than unexposed children for up to 4 weeks after conclusion of treatment. Stewart et al. [17] revealed that antibiotic treatment reduced the abundance of *Escherichia* sp. and increased the abundance of other members of the family *Enterobacteriaceae*. Antibiotics may reduce microbial diversity, and are associated with recurrent *Clostridium difficile* infection and other disease states [18]. These changes can occur rapidly in a few days after the start of antibiotic treatment, and complete reconstitution of the initial bacterial composition may not be achieved [19]. The long-term effects of these changes remain not well elucidated but are definitely not negligible. In a murine asthma model, vancomycin use in neonatal mice reduced microbial diversity, shifted the composition of the bacterial population, and enhanced asthma severity [20]. Moreover, a recent study revealed an association between exposure to broad-spectrum antibiotics before 2 years of age and childhood obesity [21]. This implies a perpetual effect of antibiotics on the gut microbiota and its metabolic modulation.

Contributions of the human gut microbiota

To establish a normal gut microbiota in early life is important not only in early stages but also in later life. A normal gut microbiota is important in at least the following aspects:

- *Nutrition*. It is well known that the gut microbiota synthesizes several molecules, such as vitamin K and constituents of vitamin B. The human body benefits from these nutrients. Similarly, carbohydrate fermentation leads to the production of short-chain fatty acids that are utilized by the host. Protein fermentation, on

the other hand, gives rise to phenolic metabolites that may need to be detoxified by the host intestine or the liver before they cause harm to the host [22]. In short, the gut microbiota heavily influences host nutrition; the microbes produce metabolites that are related to human health and metabolism.

- *Protection from pathogens*. A nonpathogenic microbiota dominance signature reduces the likelihood of disease onset caused by pathogens. In vitro studies have shown that adhesion of pathogens to intestinal mucosa was inhibited and replaced by a mixture of probiotics [23]. A gut microbiota behaving as a barrier against invasions of pathogens is one of the major physiological functions for human health. The protective effect of the gut microbiota comes not only from competition, but also from other mechanisms. For example, by using a mouse model, we showed that antibiotic-induced enteric dysbiosis predisposes systemic dissemination of both antibiotic-resistant and commensal enterobacteria through transcytotic routes across epithelial layers [24].
- *Maturation of immune responses*. Postnatal maturation of the human immune system is closely influenced by exposure to various microorganisms. The gut consists of substantial lymphoid tissue and harbors the largest abundance of microorganisms. Early intestinal colonization with *Escherichia coli* and *Bifidobacterium* is associated with higher numbers of $CD27^+$ memory B cells in infancy [25]. In addition, *Bacteroides* spp. may affect the balance of the T helper 1 (T_h1) and T helper 2 (T_h2) cell immunity in early infancy [26].

  The abundance of bacteria and also the diversity of the bacteria account for the maturation of the immunity. Low gut microbiota diversity in early infancy is associated with increased risk of subsequent allergic diseases, such as asthma [27]. Repeated exposure to different bacterial antigens would enhance the development of immune regulation through inhibition of responses to inappropriate targets, such as gut contents and allergens [14].

Diseases associated with dysbiosis

More and more diseases are being listed as being linked to the dysbiosis of the microbiota. Some important pediatric diseases are given in the subsequent sections as examples (Fig. 1).

Necrotizing enterocolitis

Classic necrotizing enterocolitis (NEC) is a disease seen in premature babies. This disease is characterized by extensive intestinal tissue necrosis and elevated serum levels of proinflammatory cytokines. Bacteremia and endotoxemia are also common [28]. Increased intestinal permeability in premature babies might promote bacterial translocation and account for the endotoxemia and bacteremia.

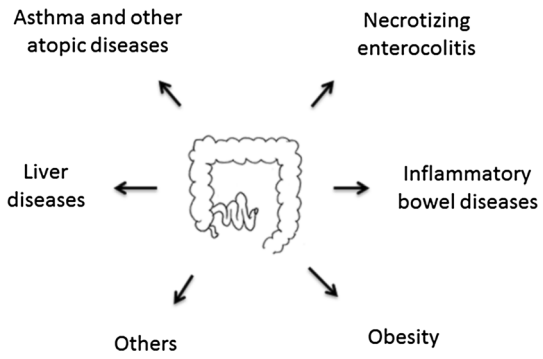

Fig. 1 Diseases associated with an aberrant neonatal gut microbiota

The gut microbiota is closely related to the occurrence of NEC. In a longitudinal follow-up study of the gut microbiota in preterm twins, a reduction in diversity of the gut microbiota and increasing dominance of *Escherichia* sp. were found before the occurrence of NEC. This phenomenon was not observed in healthy twins without later development of NEC [17]. Another longitudinal follow-up study using culture-independent technologies found that the composition of the microbiota differed significantly in NEC cases and controls 1 week before NEC diagnosis [29]. An increase (34 %) of the abundance of *Proteobacteria* and a decrease (32 %) of the abundance of *Firmicutes* were found in NEC cases between the 1 week and less than 72 h samples [29]. Claud et al. [30] found that whereas healthy preterm infants began converging to a term-like profile at around 6 weeks of age, preterm infants with NEC had overgrowth of *Proteobacteria* at the expense of *Firmicutes*, in addition to a reduction in the abundance of lactose fermenters from the family *Veillonellaceae*. These studies confirm the composition of the microbiota changes before the onset of NEC, suggesting causal roles of dysbiosis in NEC.

In addition to prematurity, antibiotic use and formula feeding have also been identified as risk factors for development of NEC [31, 32]. Both of these factors favor the development of dysbiosis and make premature babies susceptible to NEC.

As pathogenic microbials are important in NEC, introduction of nonpathogenic commensals is supposed to reduce NEC incidence. Studies in mice showed feeding of *Bifidobacterium* indeed improved gut barrier integrity and diminished NEC incidence [33]. *Bifidobacterium*, which is supposed to be protective against NEC, is abundant in

breast milk. This suggests a lower incidence of NEC in breast-fed premature babies, which is related to the gut microbiota signature.

Inflammatory bowel diseases

The incidences of inflammatory bowel diseases (IBD) are higher in Europe and the USA than in Asia [34]. Genetic studies have identified hundreds of risk alleles associated with both ulcerative colitis and Crohn's disease. However, the incidences of IBD are increasing worldwide, suggesting they are not solely genetic diseases. Environmental factors, in addition to genetic factors, are also linked to IBD. Stress, diet, infections, and smoking are frequently mentioned as environmental factors predisposing to IBD. Dysbiosis is also associated with all these factors, and may account for the occurrence of IBD.

Critical roles of the gut microbiota in IBD development have often been proposed. Studies have shown that the composition of the gut microbiota in individuals with IBD differs from that of healthy individuals in terms of phylogenetic diversity and relative abundances of microbial taxa [35]. The proportions of *Firmicutes* and *Bacteroidetes* are reduced in IBD patients, whereas the proportion of *Proteobacteria* is increased [36]. Evidence suggests IBD may result from abnormal immune reactions induced by an altered gut microbiota. Anti-inflammatory effects of *Faecalibacterium prausnitzii* were demonstrated by cytokine studies in a murine experimental colitis model in mice [37]. Loss of anti-inflammatory bacteria, rather than gain of certain virulent bacteria, may lead to bowel inflammation.

Obesity

Obesity is also becoming more and more prevalent. The prevalence and severity of obesity cannot be attributed to overeating alone. Accumulating evidence suggests that an altered gut microbiota driven by early-life dietary intake modifies host metabolism and results in obesity later. For example, the bifidobacterial numbers in fecal samples during infancy, as assessed by fluorescence in situ hybridization with flow cytometry, were higher in children who remained at normal weight than in children who became overweight [38].

In the agriculture industry, subtherapeutic doses of antibiotics have been widely used as growth promoters. The mechanisms underlying these correlations remained unexplained until recent studies revealed changes in the gut microbiota in livestock may account for the results. A murine animal study by Cho et al. [39] showed administration of subtherapeutic antibiotic doses increased adiposity in young mice and increased hormone levels related to metabolism. Subtherapeutic antibiotic doses are sufficient to alter the gut microbiome substantially, resulting in copy number changes of key genes involved in the metabolism of carbohydrates to short-chain fatty acids, increases in colonic short-chain fatty acid levels, and alterations in the regulation of hepatic metabolism of lipids and cholesterol [39]. These studies show control of metabolic homeostasis is possible by manipulating the early-life gut microbiota through antibiotic use. In the USA, the states with the highest rates of antibiotic use also have the highest obesity rates [40], suggesting mechanisms similar to those that exist in livestock may also exist in humans.

Asthma and other atopic diseases

The prevalence of allergic diseases such as asthma and allergic rhinitis is continuing to rise in countries where living conditions and hygiene standards are improving. It was proposed that higher sanitation standards and smaller household size are likely responsible for a decrease in early exposure to microbial antigens at the expense of immune development [41, 42]. The mechanisms underlying the reverse relationship between contact with microorganisms and development of allergic diseases may be related to the gut microbiota. The immature immune system is inclined toward a T_h2 phenotype in the neonatal period in a mouse model. With the establishment of a normal gut microbiota, there is a shift toward a T_h1 and T_h17 dominated immune phenotype, suggesting the immune cells in the gut require microbiota-derived cues for their normal differentiation [43].

In a study by Kalliomäki et al. [44], the gut microbiota from 76 infants at high risk of atopic diseases was analyzed at 3 weeks and 3 months of age. The results showed atopic subjects had more clostridia in their stools than did nonatopic subjects, suggesting the importance of the indigenous gut microbiota for the maturation of human immunity to a nonatopic mode. Some other studies showed bacterial diversity seems to be more important than specific bacteria taxa [45].

Again, artificial formula feeding, antibiotic use, and strict hygiene practices may lead to inadequate establishment of the gut microbiota and an increase in the incidence of allergic diseases. Some clinical, epidemiological, and experimental evidence supporting changes in the gut microbiota predispose to allergic diseases is listed in Table 1.

Liver diseases

The microbiota in the gut may have great influence on the liver since microbial products constantly enter the liver through the portal vein. Normally, small amounts of intestinal microbes and/or their metabolites entering the liver

Table 1 Clinical, epidemiological, and experimental evidence supporting perturbations in the gut microbiota predispose to asthma or other allergic diseases

Evidence	References
An inverse relation between microbial exposures and development of asthma/hay fever	[41, 42]
A positive correlation between increased use of antibiotics and increased risk of asthma/allergies	[20, 46]
Correlations between altered fecal microbiota composition and asthma/atopic eczema	[27, 47]
Success in prevention or reduction of atopic diseases by use of oral probiotics	[48, 49]

are eliminated by Kupffer cells. When the function of intestinal epithelial cell tight junctions is impaired, bacterial translocation and enhanced entry of bacterial metabolites into the liver may lead to liver diseases [50]. A recent study with a hydrodynamic transfection mouse model showed the gut microbiota contributes to the age dependence of hepatitis B virus clearance. Sterilization of the gut microbiota from 6 to 12 weeks of age using antibiotics prevented adult mice from clearing hepatitis B virus [51]. In subjects with liver cirrhosis, the composition of the gut microbiota is different. The prevalence of *Enterobacteriaceae* and *Streptococcaceae* is higher, whereas that of other bacteria such as *Bifidobacteria* and *Lachnospiraceae* is lower [52]. Impairment of normal bile secretion and portal hypertension can cause dysbiosis, which in turn influences normal liver functions. In patients with severe liver cirrhosis, hepatic encephalopathy is a common complication. Hepatic encephalopathy is caused not by organ damage but by toxic substances produced by the gut microbiota. *Alcaligeneceae*, *Porphyromonadaceae*, and *Enterobacteriaceae* were strongly associated with cognition and inflammation in patients with hepatic encephalopathy [53]. The gut microbiota was also reported to alter the risk of hepatocellular carcinoma (HCC) development in a mice model. Intestinal colonization by *Helicobacter hepaticus* was sufficient to promote aflatoxin-induced and hepatitis B virus transgene induced HCC [54]. The gut microbiota did not promote HCC by bacterial translocation to the liver nor induction of hepatitis. Instead, *Helicobacter hepaticus* in the gut activated nuclear factor κB regulated networks associated with innate and T_h1-type adaptive immunity both in the lower gastrointestinal tract and in the liver [54].

Probiotics and prebiotics

Numerous microorganisms such as *Lactobacillus rhamnosus* GG, *Lactobacillus reuteri*, bifidobacteria, and certain strains of *Lactobacillus casei* or *Lactobacillus acidophilus* have been used in food such as fermented milk products, or have been investigated for medicinal use. Such preparations are known as "probiotics." In other circumstances, indigestible food ingredients or substrates stimulate the growth and activity of certain desired gut microbes and hence benefits the host's health. These ingredients are called "prebiotics." Synergistic combinations of probiotics and prebiotics are called "synbiotics." A synbiotics containing *Bifidobacterium longum* and inulin–oligofructose growth substrate was used with success in a double-blinded randomized controlled trial for patients with ulcerative colitis [55].

Studies have shown that probiotics can benefit humans by many means. For example, they can downregulate proinflammatory cytokines by inhibiting proinflammatory nuclear factor κB and increasing expression of cytoprotective heat shock proteins [56], inducing mucosal immunoglobulin A production and providing protection against respiratory influenza virus infection [57], restoration of the gliadin-induced epithelial barrier disruption and enhancing intestinal epithelial integrity [58], and affecting pain perception and gut motility by targeting sensory nerves in the nervous system [59].

A more aggressive form of gut microbiota treatment is fecal microbiota transplantation. Studies have shown a surprisingly good response in treating recurrent *Clostridium difficile* infections, colitis, and irritable bowel syndrome [60]. Identification of more specific microbes (probiotics) or their growth factors (prebiotics) would be of great interest for different disease settings in the future. As an infant's gut microbiota is closely related to the mother's microbiota, manipulating the maternal microbiota may be a safe and effective alternative approach to decrease the risk of allergic and noncommunicable diseases in the future [61].

Functional metagenomics

How the gut microbiota interacts with host cells and affects their functions remained to be elucidated. With the help of advanced technologies such as next-generation sequencing, high-throughput screening, and bioinformative analysis, complex metabolic activities and the physiology of the gut microbiota are gradually being disclosed. One example is that a unique salt tolerance locus, *stlA*, was identified from the human gut microbiome by functional screening of metagenomic libraries [62].

Evidence is also accumulating that genes carried by bacterial cells could affect eukaryotic cell signaling and physiology [63]. For example, two *Bacteroides* genes encoding the ATP binding cassette transporter and lipoproteins that are possibly involved in bacterial-induced nuclear factor κB activation were identified [64]. Although studies on interactions between the gut microbiota and hosts are booming, the current understanding is fragmentary. The functional metagenomic approach will continuously highlight the molecular mechanisms underlying gut microbiota–host interactions.

Conclusion

Humans and their microbiota are fellow travelers in their life journeys. We harbor, nourish, and collaborate with numerous microbes within our bodies and on our body surfaces. On the one hand, they communicate and compete with each other. On the other hand, they collectively participate and influence host human physiology and lead to disease status. However, questions remain as to whether the microbiota alterations are direct causes of a specific disease and how they result in a specific disease. Currently, manipulation of a specific gut microbiota to treat specific diseases is still far from reality. The interrelationship among the diet, the microbiome, the immune system, and human diseases will be a hot topic for years to come.

Conflict of interest The authors declare that they have no conflict of interest.

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