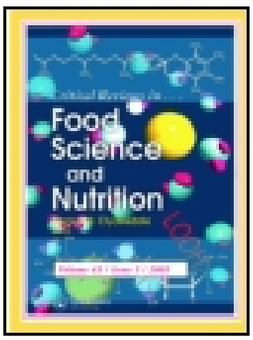

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Early-Life Food Nutrition, Microbiota Maturation and Immune Development Shape Life-Long Health

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Early-life food nutrition, microbiota maturation and immune development shape life-long health

Abstract:

The current knowledge about early-life nutrition and environmental factors that affect the interaction between the symbiotic microbiota and the host immune system has demonstrated novel regulatory target for treating allergic diseases, autoimmune disorders and metabolic syndrome. Various kinds of food nutrients (such as dietary fiber, starch, polyphenols and proteins) can provide energy resources for both intestinal microbiota and the host. The indigestible food components are fermented by the indigenous gut microbiota to produce diverse metabolites, including short-chain fatty acids, bile acids and trimethylamine-N-oxide, which can regulate the host metabolized physiology, immunity homeostasis and health state. Therefore it is commonly believed early-life perturbation of the microbial community structure and the dietary nutrition interference on the child mucosal immunity contribute to the whole life susceptibility to chronic diseases. In all, the combined interrelationship between food ingredients nutrition, intestinal microbiota configurations and host system immunity provides new therapeutic targets to treat various kinds of pathogenic inflammations and chronic diseases.

Key words: early-life nutrition; gut microbiota; immune development; allergic diseases; autoimmune disorders; metabolic syndrome

1.Introduction

The indigenous gut microbiota of mammalian infant is obtained during the delivery process from the contact with mother birth canal, therefore the composition and configuration of the newborn infant gut microbiota community have intimate relation with the microbiome distributed in mother canal and the surrounding environment (Savage, 1977). The immense number of symbiotic microorganisms inhabiting in the host gastrointestinal tract provide many extra beneficial functions, which the host genome can't accomplish but are proved to be essential for body health (Blaser, 2006). For example, gut microbiota can help to ferment indigestible plant polysaccharides and produce short-chain fatty acids (SCFA), moreover commensal gut microbiota can also metabolize dietary polyphenols and help to synthesize vitamins (Zhang et al., 2015). Hence, the consumed food style shapes the host gut microbiota structure and regulates host immunity homeostasis (Blaser, 2017; Jain and Walker, 2015).

According to the hygiene hypothesis, global epidemiology investigation revealed that larger families could lower the prevalence of hay fever, asthma, eczema and other allergic disease (Strachan, 1989; Strachan, 2015). Commonly usages of antibiotics, vaccines and triclosan have significantly decreased many kinds of infectious disease, however, the reduced diversity and richness of the human microbiome might have caused the increasing emergence of chronic diseases, such as obesity, diabetes, asthma,

hypertension, atherosclerosis, allergic rhinitis and other autoimmune disorders (Blaser and Falkow, 2009). The disappearing microbes hypothesis proposed that modern industrialization and improved sanitation had already caused the diminishing of certain species of symbiotic microorganisms which ever coevolved with human ancestors even during hunter-gather period. The missing of these symbiotic microorganisms are making obvious influences on human immune, respiratory, neurological and reproductive systems (Blaser, 2006; Blaser and Falkow, 2009; Bokulich et al., 2016).

The acquisition and colonization of gut microbiota are mainly determined by the maternal microbiome configuration, however, the taxonomic composition and abundance structure of the gut microbiota are intensely affected by the dietary structure changes and the contacting surroundings in early life. At about 3 years old, the maturation of children gut microbiota reaches a similar level to adult gut microbiota structure, after then food adaption will play critical roles on the microbial changes (Savage, 1977; Bokulich, 2016). The symbiotic gut microbiota can help to alter and modify various xenobiotics, such as dietary components, environmental chemicals and pharmaceuticals (Koppel, 2017). In fact, several metabolic diseases and autoimmune disorders susceptibility can be altered by food consumptions through modulating the gut microbiota structure and interfering the immunity homeostasis (Jain and Walker, 2015).

Nowadays, the knowledge to the interactions between food ingredients and gut microbiota configurations would affect the strategies about food production and processing technology to enhance diet nutritional value and improve human well-being

(Barratt et al., 2017), especially for the neonatal and pediatric populations, the gut microbiota and immune system of whoms were extremely sensitive to food and environment conditions (Frei et al., 2012). Therefore, the enhancements of dietary nutritional level in early life to regulate gut microbiota composition and improve immunity development are beneficial for long life health state.

2. Antibiotics treatment, early life nutrition and delivery mode shape the patterns of infant gut microbiota

Perturbation of early-life microbiome establishment by antibiotic exposure, cesarean section and formula feeding could intensively disrupt host immune development and induce allergic diseases and chronic disorders in later life (Blaser, 2017; Bokulich et al., 2016). In fact, short-term gut microbiome composition changes were induced in children treated with antibiotics, however, the bacterial diversities were found to decrease in the condition of both species and strains level, while some species were usually dominated by single strains (Yassour et al.,2016). Previous studies revealed that maternal intrapartum antibiotic prophylaxis (IAP) could induce dysbiosis of infant gut microbiota and cause long-term health consequences, however, the beneficial effects of breastfeeding might modify the disturbed infant gut microbiota and reduce the frequency of infections and other prevalent health problems among children (Korpela et al., 2016; Azad et al., 2016).

The beneficial effects of breastfeeding might be associated with the transfer of *bifidobacteria* from the mother to the newborn at the strain level, however the strains isolated from each family were quite different from clusters of other families,

indicated that each mother-infant pair have special family-specific transfer strains (Makino et al., 2011). The establishment and development of the neonatal gut microbiota immediately after birth might be influenced by unique compounds in mother milk, and these bifidobacterial species were believed to be genetically adapted to utilize specific glycans in mother milk. Therefore, early life gut microbiota maturation developed the strategies to shape the infant gut microbiota composition by exploring various functional foods (Milani et al., 2017).

Numerous evidences have demonstrated that delivery mode could influence the diversity and colonization pattern of the infant intestinal microbiota during infancy, commonly the gut microbiota of children born by vaginal delivery was dominated by *Bacteroides*, whereas children born by cesarean section lacked *Bacteroides* in the first year of life. Therefore, manipulating and promoting the origin of pioneer bacteria and the environmental factors that influence the maturation of gut microbiota during infancy should be highlighted. Healthy gut microbiome could promote the infant immune system development and maturation, and the abnormal gut microbiome might cause gastrointestinal infections (Rutayisire et al., 2016). In this respect, early childhood was considered as a crucial age-window for the maturation of gut microbiome and the prevention of various disease, since the development of a beneficial microbiota in early life was related with maternal, environmental, and host factors (van Best et al., 2015).

3. Associations between gut microbiota and modern diseases

Nowadays, the changed life style and industrialized civilization have enhanced the prevalence of allergic diseases, which might associate tightly with the reduced contacting of environmental microbes and the multiple disturbances of intestinal immune development (Strachan, 2000). Actually, the altered infant gut microbiota composition and the disturbed immune system development in early life would enhance disease susceptibility in later life (showed in figure 1), therefore programs and policies targeting the critical window of early-life gut microbiota establishment should be advanced to protect and promote whole life health (Daelmans, 2016; Machel, 2016; Black et al., 2017).

3.1 Obesity

Animal experiments have proved that subtherapeutic level of antibiotics treatment could improve infant animal growth, while the growth promoting mechanism might relate with the inhibition of pathogens colonization and the enhanced absorption of diet nutrients (Iizumi et al., 2016; Cho et al., 2012). Through affecting the richness and community structure of the gut microbiome, antibiotics treatment promoted the host fat accumulation and weight gain by specific microbial taxa colonization (Flint, 2012; Liou and Turnbaugh, 2012). Bäckhed et al (2004) reported that when germ-free (GF) mice were transferred with normal animal microbiota, 60% body fat increase and insulin resistance were observed even accompanied with a reduced food intake. Despite the changes of energy metabolism and body fat accumulation, antibiotics treatment

could also affect metabolic endotoxemia and the plasma concentration of lipopolysaccharide (LPS) by interrupting the gut microbiota composition, while low-grade chronic inflammation was commonly regarded as the molecular causality of obesity, insulin resistance and diabetes (Cani et al., 2008). To investigate the correlation and causality between gut microbiota and obesity, Koch's postulates and metagenome-wide association study were used to identify the obesity associated bacteria species, fortunately, LPS endotoxin-producing Enterobacter cloacae B29 and glutamate-fermenting Bacteroides thetaiotaomicron had been isolated from the gut microbiota of obese individuals (Fei and Zhao, 2013; Liu et al., 2017).

3.2 Diabetes

Recently, the epidemiology and prevalence of obesity, diabetes and other cardiovascular diseases are becoming a major risk factor for public health, moreover, the increasing trends of diabetes prevalence in future will still be a serious problem. An underestimate of worldwide diabetes reveals that the prevalence of all age-groups will reach 4.4% in 2030, which means there will be about 366 million diabetic people (Liu et al., 2017; Wild et al., 2004). The co-evolution of gut microbiota and their host began since the hunter-gatherer stage, and the symbiotic interactions between the gut microbiota and the host gastrointestinal tract had always been affecting host diabetes by influencing the homeostatic relationship of food intake and energy metabolism (Diamond, 2003; Filippo et al., 2017). The disturbance of early-life microbiome colonization caused by antibiotics treatment could disrupt the host immune development, and the T-cell-mediated destruction of insulin-producing beta-cells

could increase the host's risk of suffering from juvenile (type 1) diabetes (Li et al., 2008; Candon et al., 2015). Considering about the genetic and environmental factors that influenced the type 2 diabetes susceptibility, the thrifty genotype hypothesis indicated that "fast food adaption and fat storage" were survival advantages which emerged through long-term natural selection, while the thrifty phenotype hypothesis believed that pancreas islet cell dysfunction and peripheral insulin resistance were metabolic adaptations which were programmed even since fetal malnutrition (Prentice et al., 2005; Baschetti, 1998; Cai et al., 2015; Tilg and Moschen, 2014). As an important environmental factor, intestinal microbiome play a critical role for early-life host immune system development and diabetes susceptibility.

3.3 Atopy and allergic diseases

The prevalence of human allergic diseases (including asthma, allergic rhinitis and allergic dermatitis) has risen sharply worldwide, and it is believed that manipulation of the intestinal microbiota during early life may alter host immunity homeostasis and increase the risk of childhood allergic diseases (Ferreira, 2014). The contacts of host immune system with the commensal microorganisms in early life helped to train immune cells to respond properly to pathogenic antigens, however the hygiene hypothesis proposed that the modern modified lifestyles might have caused deficient immune response and impaired immune tolerance to the intestinal microbiota (Rook, 2012).

Asthma is a kind of chronic respiratory disease which shows excessive airway smooth muscle contraction and elevating mucus production, and epidemiological studies

showed that asthma was affecting approximately 300 million worldwide people (Ferreira, 2014). Perturbations of the gut microbiota composition have been certified for the development of allergies, for the reason that asthmatic children have a quite different intestinal microbiota structure while compared to children without asthma. For example, children with asthma have a high abundance of pathogenic *Clostridium difficile* and low richness of *Bifidobacterium* and *helicobacter pylori*. Therefore, early life colonization of *Helicobacter pylori* might be inversely related to the risk of childhood asthma (Chen and Blaser, 2008; Reibman et al., 2008; Chen and Blaser, 2007). On the condition of childhood acquisition of *Helicobacter pylori* before 10 years old, the risk of allergic rhinitis symptoms are reduced. Atopic dermatitis was a kind of allergen-specific skin disease during which showed exacerbated skin sensitization to pollens or molds, in fact, allergic dermatitis could be considered as a systemic problem involved with the gut microbiota dysbiosis and the increased intestinal permeability (Craig, 2016).

Perturbations of the commensal microbiota composition in early life have been proposed as a disturbance of host immune system and may increase the prevalence of asthma, allergic rhinitis and allergic dermatitis. Hence, proper microbial exposures in early life had been considered to have protective effects for modifying atopy, moreover, supplementation with probiotics and prebiotics was also considered as effective treatment to prevent children atopic diseases (Chen and Blaser, 2007; Craig, 2016; Holster et al., 2012).

3.4 Psychiatric diseases

Emerging studies revealed that gut microbiota could achieve bidirectional communication and interaction with the brain, by acting on brain neurodevelopment and function. The commensal gut microbiota had been proved to play critical roles in anxiety, depression, cognition, autism spectrum disorder (ASD) and other psychiatric diseases (Sharon et al., 2016; Kennedy et al., 2016; Macqueen et al., 2017). Research data revealed that the gut microbiota altered the formation of blood-brain barrier (BBB), neurogenesis and other neurogenerative process to modulate host brain function and behavior. The bidirectional communication and interaction between intestinal flora and brain were involved in neural, endocrine and immune connections, therefore a microbiota-gut-brain axis was formed and provided a new clinical therapeutic target for central nervous disorders (Marilia et al., 2015). Germ-free animal models, prebiotics, probiotics, antibiotics, functional food and other technical strategies have been applied to investigate the association between gut microbiome dysbiosis and psychiatric disorders. Much current work revealed that westernized diet and life style could cause immunologic, neuronal and endocrine changes and could induce epidemiological obesity and mental illness. Hence, dietary therapies towards microbiota-gut-brain axis for microbiome configuration modulation could be explored to promote host mental development and brain function and to treat all kinds of mental diseases (Ochoa-Repáraz and Kasper, 2016).

3.5 Food allergy

The number of cohort who are sensitive to food allergens is increasing, especially for the severe allergic reactions induced by plant derived food allergens, such as wheat

gluten, peanut and peach protein (Skypala, 2017). The development of food allergic disease was predominately associated with early-life exposure to environmental factors and formula feeding, which mainly caused by the imbalance of Th1/Th2 cytokine production and the altered allergic sensitization mediated with IgE immune response (Rjjv and Savelkoul, 2017; Reynolds and Finlay, 2017). However, the gut microbiome played a critical role in early life immune system development, because specific modulations of the gut microbiota dysbiosis and their relative metabolites could be used as effective strategies to reduce the incidence of functional gastrointestinal tract diseases affected by food allergy (Aitoro et al., 2017). Fruits and vegetables juices, new processing technologies to reduce food allergenicity and management of early-life exposures to environmental factors could provide beneficial changes for host immune tolerance and promote protective effects to prevent food allergy (Jones and Burks, 2017).

4. The interactions between food nutrients and gut microbiota

The composition of gut microbiome community was affected rapidly by dietary structure changes, therefore the related interactions between gut microbiota and diet chemicals could be considered as novel therapeutic targets for personalized nutrition and medicine application to promote host health (David et al., 2014; Brüssow and Parkinson, 2014). Studies revealed that the host physiological state was intimately regulated by food ingredients and the indigenous gut microbiota, even short-term

dietary changes could obviously regulate gut motility through acting on the gut microbiota and the enteric nervous system (Dey et al., 2015; Waldron, 2015).

4.1 The alteration of intestinal microbiota structure modulated by food consumption

Food nutrients are the major energy resources for human growth and development, and the gut microbiota inhabiting in the colon can influence the nutrients energy harvest, the vitamins synthesis and the drugs metabolism. The co-evolutionary history of the symbiotic gut microbiota and human demonstrated that dietary composition changes and food choices contributed to the enterotypes formation and essential physiology evolution from hunter-gatherers to modern living people (He et al., 2013). By comparing children intestinal microbiota shaped separately by the modern western diet and the ancient rural diet, the preserved diversity of gut microbiota was believed to be able to protect host from avoiding various inflammations and colonic diseases (Filippo et al., 2017; Carlotta et al., 2010; Crittenden and Schnorr, 2017). Prebiotic food ingredients (such as dietary fiber, polyphenol and polysaccharide) contained in fruits, vegetables, whole grains and teas were identified be able to stimulate the growth of beneficial bacteria and inhibit pathogenic bacteria colonization (Ming et al., 2017). Consumption of apple polysaccharide lowered the abundance of *Firmicutes* and *Fusobacteium* and enhanced the richness of *Bacteroidetes* and *Lactobacillus*, moreover, apple dietary fiber and flavone were prove to have positive relationship with *Blautia*, *Lactobacillus*, *Bifidobacterium* and *Faecalibacterium*. Diet that contained plant polysaccharides could enhance the abundance of *Roseburia*, *Eubacterium rectale* and *Ruminococcus bromii*, while diet

composed of animal meat could increase the abundance of *Alistipes*, *Bilophila* and *Bacteroides* (David et al., 2014). Wu et al.(2011) and Liang et al. (2017) had proved that human fecal communities were clustered into several enterotypes which were strongly affected by dietary structure, and the enterotypes were distinguished mainly by abundance of *Bacteroides* (shaped by protein and animal fat) and *Prevotella* (shaped by carbohydrates). Therefore, the impact of diet ingredients on the gut microbiota involved intimately with the health promotion and disease pathogenesis (Bushman et al., 2013).

4.2 The transformation of food ingredients metabolized by gut microbiota

The gut microbiome contained diverse and complex community of bacteria, archaea, fungi and other symbiotic microorganisms, and the metabolic products (such as essential vitamins, short-chain fatty acids and other nutrients) generated by microbes benefited the physiological process and the growth of both gut microbiota and their host (Koppel et al., 2017). The gut microbiota inhabited in gastrointestinal tract encoded a broad diversity of enzymes, therefore the increased abundance of *Akkermansia*, *Bifidobacteria*, *Lactobacillus*, *Bacteroides* and *Prevotella* regulated the synthesis of health and disease related metabolites, such as short-chain fatty acids (SCFAs), bile acids (BAs), trimethylamine-N-oxide (TMAO) and lipopolysaccharides (Lyu et al., 2017).

The indigestible carbohydrates (such as dietary fiber and resistant starch) which can’t be digested by the host enzymes in the upper gut could be fermented into

SCFAs (acetate, propionate and butyrate) in the cecum and colon. Besides the energy supplying effects, SCFAs could also act an important role in activating G-coupled-receptors (GPR41 and GPR43), decreasing inflammatory response and increasing epithelial barrier function (Ferrario et al., 2017; Koh et al., 2016). Previous study revealed that chronic or intermittent deprivation of dietary fiber could cause colonic mucus barrier dysfunction, therefore dietary fiber could be exploited to protect the colonic mucus barrier by inhibiting the mucosal pathogen (Desai et al.,2016; Gazzaniga and Kasper 2016).

Under the condition of dietary fibers in short supply, amino acids degraded from dietary proteins or endogenous proteins could be metabolized as complement energetic resources (Koh et al., 2016). Numerous amino acids metabolites were synthesized and produced from protein metabolism by gut microbes, which might induce both beneficial and harmful physiological effects on their host. Branched-chain fatty acids (such as isobutyrate, isovalerate and 2-methylbutyrate) which originated from branched-chain amino acids (valine, isoleucine and leucine) might induce chronic metabolic diseases, however, metabolites generated from aromatic amino acids (tryptophan, phenylalanine and tyrosine) might demonstrate beneficial effects on systemic immunity, colonic epithelium renewing and intestinal permeability (Portune et al., 2016; Blachier et al., 2007; Dodd et al., 2017). Therefore, different dietary protein sources had inconsistent impacts on the gut microbiota composition, and the interactions of dietary proteins with oligosaccharides and other

food ingredients on gut fermentation should also be regarded (Zhu et al., 2017; Bai et al., 2016).

Plant derived polyphenols compounds had been proved to be able to play essential roles in maintaining antioxidant activity, antimicrobial activity, antitumor activity and other important biological activities (Valdés et al., 2015). There were thousands kinds of polyphenol molecules widely distributed in plant derived foods, such as soy isoflavones, tea flavonoids and ellagic acids from nuts and berries, and these non-absorbable polyphenols compounds could be transformed into bioactive forms by specific intestinal microbial enzymes (Koutsos et al., 2017; Septembre-Malaterre et al., 2017; Cheng et al., 2017). These processing transformations (such as ring cleavage, demethylation and dehydroxylation) could produce more active and better absorbed metabolites than the native polyphenols compounds (Espín et al., 2017). Taken together, the interactions between dietary polyphenols and gut microbes were a two-way communications, for one hand, the intestinal microbes could catabolize the polyphenols compounds ingestion, simultaneously, the transformed phenolic metabolites could also modulate the gut microbiota composition, therefore the physiological effects resulted in potential benefits to human health (Kaakoush and Morris, 2017; Cassidy and Minihane, 2017).

5 Immune homestatosis: the equilibrium between nutrition, gut microbiota and host immunity

Accumulating evidences had proved that the complex interactions among diet, commensal intestinal microbiomes and the host immune system played critical role in host health and disease (Cerf-Bensussan and Gaboriau-Routhiau, 2010). Changes of dietary ingredients frequently induced the changes of the gut microbiome composition and their corresponding metabolites, by modulating the host immunity, the commensal microorganisms could influence the equilibrium between pro-inflammatory and regulatory responses and host systemic immune diseases (Shibata et al., 2017; Zmora et al., 2017).

The cross-talk between gut microbiota and the host immune system determined the strategies of host intestine to resist bacteria community colonization and to control the pathobionts expansion, therefore the development and maintenance of the host immune system together with the innate and adaptive immune responses could all be regulated by gut microbiota (Kim et al., 2017). Compared with the specific pathogen free (SPF) mice, the development of the gut associated lymphoid tissues (GALT) in germ free (GF) mice are remarkably delayed, therefore the exposure to commensal gut microbiota has a dynamic relationship with the development and maturation of B cells, IgA responses and the formation of mucus layer. In addition, the microbial signals from the commensal microbiota and pathobionts helped to balance the inflammatory immune responses mediated by different T cell subsets (Cao, 2017; Atarashi et al., 2017). The mechanisms of Th1-mediated inflammation responses

could be induced by antigen-presenting dendritic cells (DCs) through activating Toll-like receptor 4 (TLR4) signaling pathway, then epithelial cells could produce cytokines (such as interleukin-4,6,10,12,17,23, IFN-γ and TNF-α) to regulate the inflammatory immune response (showed in figure 2). The interactions between gut microbiota with dendritic cells and epithelial cells regulated the regulatory T-cell and effector T-cell responses during inflammation and disease (Schirmer et al., 2016; Alexander et al., 2014).

Epidemiological and experimental research data had revealed that specific gut microbiota colonization process and the microbe-host interactions which established in early life programed the risks for long-term health and disease outcomes. Environmental factors such as antibiotic treatment, stress exposure and delivery mode affected the gut microbial colonization and intestinal immune development, and showed in close interaction with life-long propensity to immune disease (Francino , 2014; Schokker et al., 2014).

6 Conclusion and future prospects

In the past few decades, numerous findings had illustrated that early-life microbiome acquisition and maturation affected the long term host well-being state. The industrialized human living conditions have perturbed and disrupted the commensal microbiome composition and have led to the increasing emergence of microbial infections, allergic diseases (such as asthma, rhinitis and dermatitis) and autoimmune diseases(Blaser, 2017; Moeller, 2017; Deehan and Walter, 2016).

The bidirectional microbial-host interactions which can be regulated by food nutrition had markedly been altered by antibiotic treatment, cesarean section and formula feeding, therefore the transmission of maternal bacteria had been perturbed and the infant microbiome diversity had been apparently reduced (Dominguez-Bello et al., 2010; Putignani et al., 2010; Kainonen et al., 2013; Makino et al., 2013). Simultaneously, the decreased exposure to environmental microorganisms had altered host immune system establishment and delayed immunity development, while the previous studies had revealed that contacts with specific microbe-associated molecular patterns (MAMPs) could trigger a series of immune reactions for infant gut maturation during the first six months after birth, termed as a "window of opportunity" (Laforest-Lapointe et al., 2017). Early gut ecological imbalance might lead to crucial taxa disappearing and reduce the community colonization resistance, therefore the incidences of many chronic and metabolic diseases were increased, and even the childhood cognitive development was disrupted in early life (Zhu et al., 2017).

Currently, proper efforts should be tried to restore the disappearing microbiome and to modify the impaired immune function. Early-life food nutrition should be highlighted to modulate gut microbial composition and regulate mucosal immunity, therefore, probiotics, prebiotics and synbiotics supplement could be considered to maintain the intestinal microbial ecosystem balance and to improve the host health conditions (Kau et al., 2011; Markowiak and Śliżewska, 2017).

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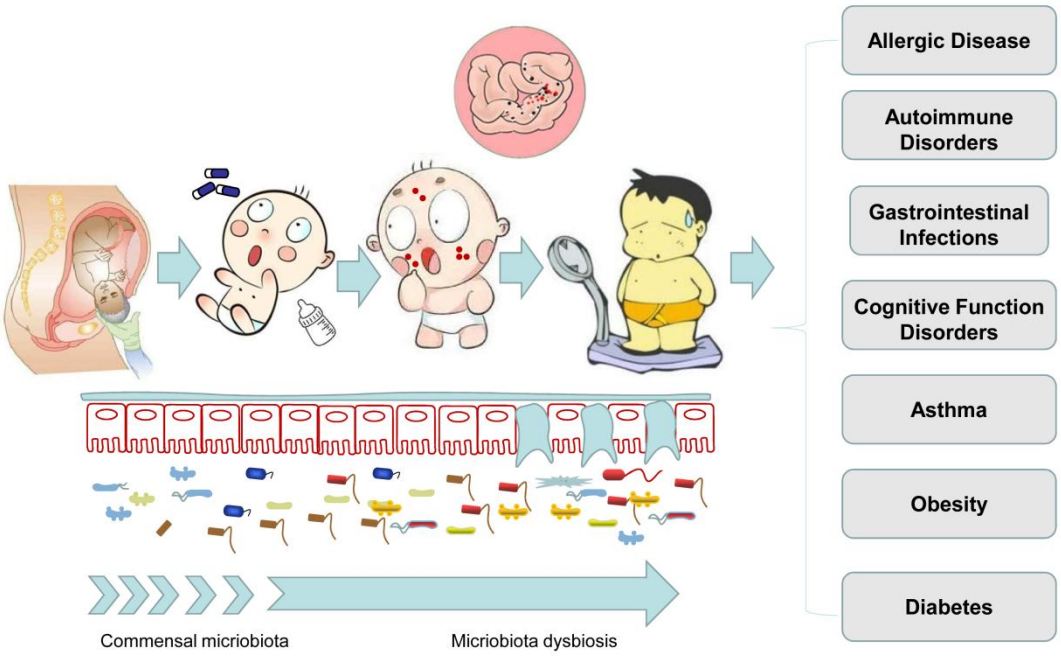

Figure 1. Diseases associated with disturbances of early-life gut microbiota colonization and the infant immune development.

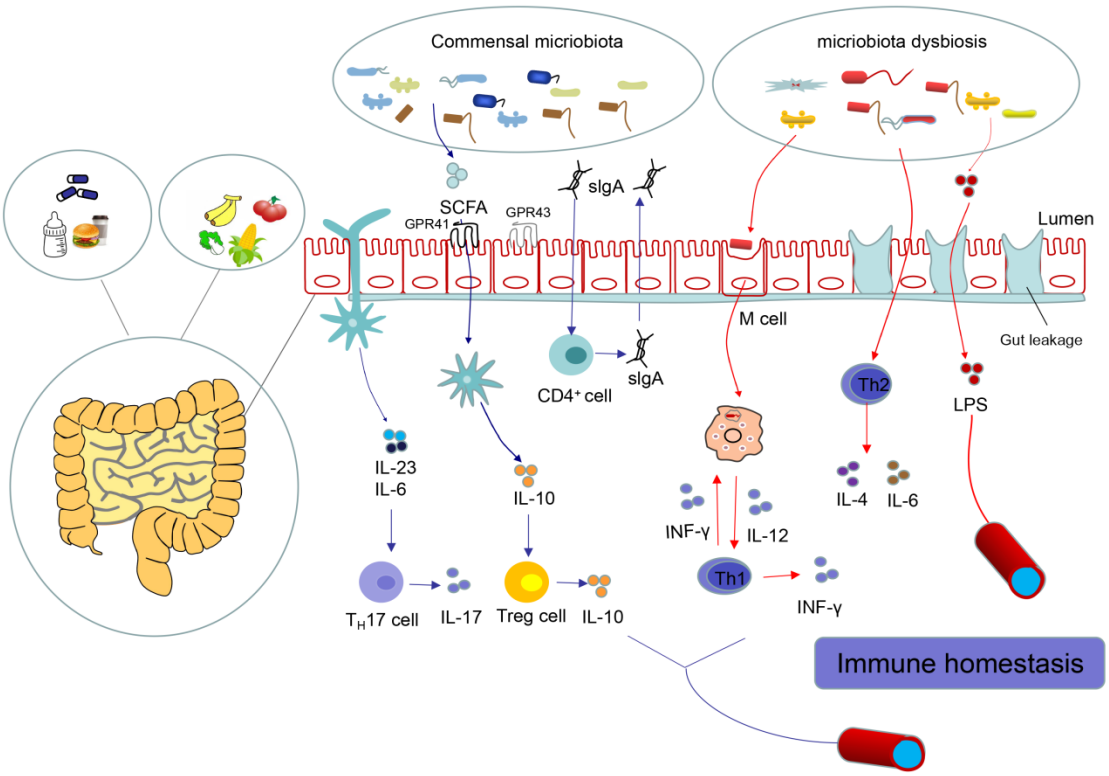

Figure 2. The interrelationships between food nutrition, gut microbiota and host immune development.