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Commensal bugs from the gut-shaping human health and disease

Abstract

Gut microbiome is a collection of symbiotic microorganisms that resides in human gastrointestinal tract. This microbiota plays essential role in immunological responses and other host activities. A plentiful of evidences suggests that the alterations of the normal gut microbiota composition are associated with various human diseases and psychological disorders. Proper knowledge about the host-microbiota interaction may reveal the underlying cause of these pathophysiological responses from gut microbiota, which in turn may provide novel insights into the importance of gut flora in human health. This understanding is essential for the development of future personalized strategies of therapeutics. The present review is an endeavor to provide an account about the human gut microbiome their diversity and disease causing capability; discussing the significance of gut microbiome in few common and widespread diseases/disorders.

Keywords: human gut microbiome, gut microbiota, *clostridium difficile* infection, obesity, autism

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Abbreviations: GI, gastro intestinal; SCFA, short chain fatty acid; CDI, *clostridium difficile* infection; CDAD, *clostridium difficile* associated disease; NSAID, non steroidal anti inflammatory drug; IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, crohn's disease; IBS, irritable bowel syndrome; SIBO, small intestine bacterial overgrowth; CRC, colorectal cancer; BMI, body mass index; NAFLD, non alcoholic fatty liver disease; ASD, autism spectrum disorder

Introduction

Human body harbors a huge number of microorganisms. Resident microbes contain ten times more cells than our own body cells and hence more number of genes than present in a human body; as a consequence they represent a combined microbial genome with a size bigger than human genome itself.[1,2] Collectively, the flora has a metabolic action equal to a virtual organ within an organ.[3] The term 'microbiome' actually refers to the whole number of microorganisms residing in human body.[1,4,5] It is different from the term 'microbiota', which describes the microbial population present in different niches in the body. Researchers at human microbiome project are sampling and exploring data from few specific sites of human body viz. airways, nasal passages, oral cavities, skin, blood, gastrointestinal tract, urogenital tract etc.[4] The microbial density starts increasing in the distal small intestine and in the large intestine it rises to an estimated of 10^{11}–10^{12} microbes per gram of colonic content which contributes to 60% of the fecal mass. Usually this microbiota is Commensal and represents a healthy asset of our body helping us to digest food and maintain immunity. Our typical understanding about a disease causing event states us that whenever a pathogenic organism enters our body the disease takes shape. Introduction to the era of human microbiome enlightens us about a more susceptible way of causing disease, the imbalance of the microbiota within our body. Therefore human microbiome can be considered as a therapeutic drug target.[6] The organisms from this microbiome are hard to culture. Metagenomics the study of the genetic material extracted directly from environmental samples in a given environment has been applied to the studies of the human microbiome, since it can be used to investigate various microbes simultaneously without cultivation. This approach has helped in taking speed in the studies of human microbiome and their medical relevance. Studies about diverse microbes from the human body site and the correlations between their composition and disease have rapidly increased our understanding towards the importance of the human microbiome and its roles in health and disease.[5,7] This bang of human microbiome data holds the promise of managing personal health based on the genome and microbiome information of an individual.

Discussion

The human gut microbiome

A new chapter in medical science has emerged with the recognition of the crucial role of the gut microbiota in health and disease. Among all the niches, human GI tract contains the most number of microorganisms. The content is so huge that sometime it is called 'the other genome' and sometime it is referred to as the 'forgotten organ'.[8] The density of the microbiota increases from the proximal to the distal gut reaching its maximum at the colon. In the different habitats of the gut ecological sorting and competitive exclusion between microbes are the key factors influencing microbial diversity.[9,10]

Components of gut microbiota

Stochastic factors during colonization and in situ evolution cause the diversity of gut microbiota between individuals.[11] The intestinal microbiota of infants lacks diversity and their major constituents are the phyla *Proteobacteria* and *Actinobacteria*. The microbiota attains diversity with age with the addition of *Fusobacteria*, *Cyanobacteria* and *Verrucomicrobia* amongst others. The dominance of *Firmicutes* and Bacteroidetes characterizes the adult microbiota.[12–14] The gut microbiota is mainly a collection of anaerobes, which outnumber facultative anaerobes and aerobic microbes by approximately 2-3 orders of magnitude.[15]

Development of gut microbiota

At the time of birth, human gut is completely sterile. However, immediately after birth the colonization of mammoth variety of microorganisms including bacteria, archaea, fungi and viruses starts within the body. The colonization of these microbial species within a body depends upon the mode of delivery, hygene level, infant diet, and medication.[16] In human, after the age of 2.5years the gut microbiota remains almost the same throughout the adult age of that individual.[17,18] The actual adult human gut microbiota composition is diverse and differs from person to person in a significant way. Therefore it has been suggested that it can be used as a substitute to fingerprinting.[19] In this regard three entero types have been found viz. *Prevotella, Ruminococcus* and *Bacteroids* that are independent of age or sex. The normal human gut flora composition is subject to age, diet, medication and socioeconomic conditions. In a recent study of gut microbiota in elderly individuals, the associations with diet and age was documented.[20] It is a prominent fact that, although there is great variety in the composition of the gut microbiota among individuals, there still lays a conserved set shared between individuals, and this set of microbiota is called the core gut microbiome.[21] The functions and pathways encoded by the core gut microbiome offer the greatest benefit to the host and are essential for the correct functioning of the healthy gut.

Role of gut microbiota in preserving health

The gut microbiota helps the host in various ways, including protection against probable pathogens, production of essential vitamins, digestion of polysaccharides, regulation of fat storage and modulation of the host's immune system.[22,23] Without gut flora, the body would not be able to make the most of the undigested carbohydrates it consumes; because gut flora have enzymes for breaking down certain polysaccharides e.g. starches, fibers, oligosaccharides and sugars, that human cells lack.[24] Bacteria turn these carbohydrates into short chain fatty acids (SCFAs) including acetic acid, propionic acid, and butyric acid. These materials provide a major source of useful energy and nutrients for host, as well as helping the body to absorb essential dietary minerals such as calcium, magnesium, and iron. Gut flora prevent the growth of pathogenic species by competing for nutrition and attachment sites to the epithelium of the colon.[25,26] Indigenous gut flora also produces bacteriocins, which are toxins that inhibit the growth of similar bacterial strains. Gut bacteria play a role in the expression of toll-like receptors in the intestines, TLRs cause parts of the immune system to repair injury caused, for example, by radiation.[24,27] Latest studies have also revealed that the gut microbiota influences brain and the gut-brain axis configures the stress related symptoms such as anxiety and pain tolerance and few other psychological conditions.[28]

Role of gut microbiota in disease/disorder

It has been well established that the human gut microbiota is essential for human health. However, an alteration of the normal composition of the gut microbiome, called dysbiosis, leads to formation of various types of diseases. Therefore it is reasonable to conclude that modulation of the gut microbiota can be used as a therapeutic target in treating these chronic diseases. Before properly utilizing the gut microbiota as a therapeutic tool, it is necessary to understand the role of these microbes in shaping disease. The dysbiosis created by the gut microbiota leads to two kinds of illnesses viz. gastrointestinal disorders and systemic conditions.[29] Till date a great number of physical and psychological disorders have been associated with the alteration of gut flora; addressing all can be quite unfeasible task for this review. Thus, in this review, brief overviews of the current understanding about the role of microbiota in few common disease and disorders have been discussed.

Gastrointestinal illnesses

***Clostridium difficile* infection:** The name *Clostridium difficile* has been associated with several major kind of gastrointestinal illness and so far, this bacterium has been detected as a leading cause of nosocomial diarrhea and antibiotic associated diarrhe.[30–34] *Clostridium difficile* is an anaerobic, gram positive, spore forming bacteria that emerges as an opportunistic pathogen if circumstances permit. *Clostridium difficile* infection (CDI) is mainly caused by enterotoxin TcdA and cytotoxin TcdB[35–39] that can cause severe diseases from nosocomial and antibiotic associated diarrhea, pseudomembranous colitis, fulminant colitis, sepsis to toxic mega colon; all of which are termed as *Clostridium difficile* associated disease (CDAD).[33,40–43] The bacterium is a minor part of gut flora and has been detected in 50% of healthy infant and 5% of adult feces.[44,45] However in certain conditions like intestinal dysbiosis, this organism can increase in number and generate disease.

The risk factor for CDI includes age, diet, prolonged hospitalization, long term antibiotic usage, presence of severe comorbidities, inflammatory bowel disease, malignant tumor, and chemotherapy.[46] However, there are studies to prove the association of gut microbiota alteration with CDI.[47] Antimicrobic drugs can alter normal gut homeostasis by decreasing carbohydrate fermenting and butyrate producing bacteria viz. bacteroids and firmicutes.[48–53] Bacteroids play a significant role in the digestion of carbohydrate in the intestinal lumen and resulting in the production of the essential substrates important for the homeostasis of colonocytes.[54,55] A reduction in butyrate producers (such as *Roseburia* and *Ruminococcus*) is observed in case of NSAID users.[56] Diet can also play a key role in the alteration in gut microbial flora. A prolonged elemental diet, i.e. a diet poor in fiber can again help in dysbiosis. All these environmental conditions and the consequent intestinal dysbiosis create such an environment that disrupts the normal protective barrier formed by the gut microbiota and hence *C. difficile* can happily grow in increased number in human body and cause disease.[52,57] The occurrence of dysbiosis in gut changes the production of substrates fermented by the anaerobic gut microbiota, including butyrate, short chain fatty acids (SCFAs), acetates, and lactates that are essential to the intestinal epithelial cell homeostasis.[58] A direct role of SCFAs to inhibit the growth of *C. difficile* was also assumed. This hypothesis has been confirmed by *in vitro* experiment, but results from *in vivo* studies do not actually support this hypothesis.[59,60]

The treatment of diarrhea normally involves the antibiotic metronidazole in case of first occurrence of the disease. For more severe conditions, vancomycin can be used, though it introduces another pathogen *Staphylococcus aureus* to intestine.[61] *Clostridium difficile* can germinate to vegetative state and the spore can arise after the antibiotic dose is ceased; hence the chances for CDI relapse increases with these antibiotic usages. As a more convenient and safer way to treat recurrent CDI, fecal microbiota transplantation has emerged.[62,63] Infusion of feces from healthy donor to the patient helps regaining the normal gut homeostasis. It has been proved to be effective in treating recurrent *C. difficile* infection, and is more

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effective than vancomycin alone.[64] It can also be used to treat other conditions like inflammatory bowel disease, irritable bowel syndrome, colitis and some neurological conditions.[65–68]

Irritable bowel syndrome: Irritable bowel syndrome (IBS) is a functional GI disorder with chronic abdominal discomfort and pain, swelling and bloating; with no identifiable organic cause.[69] IBS can be classified according to three kind of bowel habits viz. diarrhea associated IBS (IBS-D), constipation associated IBS (IBS-C), and with mixed bowel habit (both diarrhea and constipation IBS-M). Patients diagnosed with IBS are in general found to experience severe level of stress, anxiety and depression, as compared to normal healthy controls.[70] All of these comorbidities result in significantly impaired quality of living in patients. Today, IBS is the most commonly diagnosed GI disorder and is reported to affect 5%-25% of the population worldwide - throwing a big financial burden for the patients and the healthcare systems.[69,71–75]

IBS is a multifactorial disease; where genetic, neurobiological, and psychosocial factors all have almost equal importance on the etiological ground. In this regard, several hypotheses have been proposed including alteration in the gut microbiota, dysregulation of the brain-gut axis and autonomic nervous system, visceral hypersensitivity, and altered levels of gastrointestinal neuropeptides and hormones.[76–78] Recent reports confirm that quantitative and qualitative alteration of the gut microbiota contributes to this disorder. The intestinal microbiota composition is different in case of IBS patients as compared to their healthy counterparts. Intestinal microbiota can be further divided into two distinct ecosystems: luminal bacteria and mucosa associated bacteria and it has been hypothesized that the disturbances associated with the mucosa level is more significant than the pathogenesis created by luminal bacteria.[79] Most of the studies on irritable bowel syndrome have focused on the fecal samples from patients and have demonstrated the microbiota composition alteration in both adults and children. IBS patients have fewer *Lactobacillus* and *Bifdobacterium sp*.[80] These are the good bacteria in healthy controls as they bind to the epithelial cells making a competitive environment for the pathogens and enhance gut barrier functioning.[81] A significant increase in the quantity of aerobic bacteria and *Lactobacillus* was noted in IBS-D fecal samples but not in mucosal ones.[82] Elevation in the level of *Ruminococcus, Clostridium, s*species and a decrease in the quantity of *Bifidobacterium* and *Faecalibacterium* species have been demonstrated in IBS.[80,83–89] In children, a fecal microbiome characterized by a significantly high percentage of Gamma Proteobacteria and an increased number of several bacterial taxa from the genus *Alistipes* has been reported in the IBS setting.[90] Colonic gas production, associated with the bacterial fermentation of unabsorbed food substances, is greater in patients with IBS than healthy subjects.[91,92] Quantitative changes of the bacterial content in the small intestine, resulting in a clinical syndrome called small intestinal bacterial overgrowth (SIBO), has been reported in some patients with IBS.[77,93–95] SIBO results in unusual fermentation with increases in gas production and abnormal gastrointestinal motility. Quantitative changes in the colonic microbiota may lead to the increase in number of specific species that produce more short chain fatty acids (SCFAs) and gases, such as methane, hydrogen and carbon dioxide; resulting in abdominal bloating and distension. An elevation of the level of SCFAs (acetate, butyrate and propionate) leads to acidification of the colon and de-conjugation of bile acid. This in turn may cause significant changes in water and electrolyte transport in the colon which result in diarrhea.[96,97] Malabsorption of carbohydrates may cause increase in the level of hydrogen production, which is associated with diarrhea predominant IBS (IBS-D).[98] On the other hand, excess methane gas production is associated with constipation predominant IBS (IBS-C).[96] A large portion of the patients with inflammatory bowel disease also report symptoms like IBS with no proper inflammation.[99] Manipulating the microbiota through prebiotic, probiotic and antibiotic helps in gaining back the normal healthy state.

Inflammatory bowel disease: Inflammatory bowel disease (IBD) is an inflamed condition of the colon and small intestine. It is a chronic, relapsing and multifactorial disease occurring in the digestive tract; the major types being Crohn's disease (CD) and ulcerative colitis (UC).[100] Crohn's disease is characterized by aggregation of macrophages that form non-caseating granulomas whereas ulcerative colitis is diffuse mucosal inflammation that extends from the rectum. Family aggregation has been noted in IBD, where the first degree relatives are in fivefold greater risk of acquiring the disease. The inheritance is more commonly seen in CD than in UC.[101,102] Patients from IBD have activated innate and acquired immune responses and loss of tolerance to endogenous gut microbiota.[103–106]

The exact etiology of IBD is yet to be known but there lays considerable evidences to suggest the role of gut microbiome in the pathogenesis of IBD. Although the exact mechanism of IBD is not yet being fully elucidated, four broad mechanisms are proposed to explain the complex relationship between the Commensal microbiota and IBD: (i) dysbiosis of conventional microbiota; (ii) induction of intestinal inflammation by pathogens and functionally altered commensal bacteria; (iii) host genetic defects in containing Commensal microbiota and (iv) defective host immunoregulation.[107] IBD patients show reduced number of *Firmicutes* (*Clostridium clusters* IV and IX) and *Bacteroids*, but higher number of *Proteobacteria* and *Actinobacteria* as compared to normal healthy controls. Among *Firmicutes, Faecalibacterium prausnitzii* is shown to have anti inflammatory activity and is found to be significantly decreased in CD.[108,109] Furthermore, Joossens et al.[110] have shown that reduction of *Faecalibacterium prausnitzii, Bifidobacterium adolescentis, Dialister invisus*, an unknown species of *Clostridium* clusters XIVA and increase of *Ruminococcus gnavus* are characteristic features in the fecal samples of patients suffering from CD.[110] Higher levels of sulfate reducing bacteria have been found in IBD patients. These bacteria are associated with less SCFA e.g butyrate production, which is supposed to induce cell hyper-proliferation.[111] The influence of gut microbiota in IBD is furthermore supported by fecal microbiota transplantation being efficiently effective in curing patients.[112,113]

Systemic conditions

Obesity, non alcoholic fatty liver disease and type 2 diabetes: Obesity is a medical disorder in which excess body fat accumulates over body. It is only recently that the problem of obesity has achieved global response in contrast to the problem of underweight and malnutrition, which have always got clinical and social attention. World Health Organization describes obesity as one of the major public health concern that threatens the modern world civilization and of late has become a global epidemic. A person is categorized as overweight when the body-mass index (BMI) is about 25kg/m^2 or higher and people are classified as obese when the BMI is beyond 30kg/m^2.[114] Energy balance is equilibrium between the amount of energy taken in as food and the amount spent during resting metabolism, physical activity, loss in the feces and urine. The shift

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in efficiency of the body for harvesting energy from diet is created by gut microbial imbalance. A small change in energy balance over the course of a year can actually result in significant changes in body weight.[115] Obesity has serious health concerns including increased risk for type 2diabetes, cardiovascular diseases, non alcoholic fatty liver disease (NAFLD), pulmonary hypertension, asthma, sleep apnea, osteoarthritis, gall-bladder disease, a number of cancers, and most importantly an increased risk of mortality.[116-120]

It has been proposed that the composition of the gut microbiota during childhood predicts the following development of obesity in humans. In this regard some studies were conducted to compare between the fecal samples from overweight/obese and normal weight children.[121–123] It shows that during infancy a significantly higher number of bifidobacterial species was observed in children who maintain a normal weight at age 7years, while significantly greater numbers of *Staphylococcus* aureus were detected in children who became obese afterward. Therefore, it is hypothesized that an early modulation of gut microbiota can actually prevent obesity.[124,125] Interestingly, another study found that the microbiota composition is different in case of pregnant women also with relatively higher numbers of *Bacteroides* and *Staphylococcus* found in overweight pregnant women.[126] Obese human twins also have different gut microbial composition as compared to their lean twin. The obese one has reduced levels of Bacteroidetes and also less bacterial diversity.[121]

NAFLD is a multifactorial disease where fat deposition in the liver is not due to excessive alcohol use. Several lines of incidences suggest a strong association between gut microbiome and liver.[127–134] Backhed et al.[127] observed that after 15days of the transplantation of normal cecal microbiota to germ-free mice results in 60% increase of body fat along with a more than 2 fold increase in hepatic triglyceride content. Further animal studies suggest that the gut microbiota can initiate hepatic steatosis in the course of an increase in monosaccharide absorption,[127] chronic metabolic inflammatory reactions,[128,130] and modulation of bile acid metabolism.[133] Quite a few human studies have also reported that gut microbiota contributes in shaping NAFLD and that bacterial overgrowth in obese patients is a signature of hepatic steatosis.[131,132,134] Miele et al.[131] reported that NAFLD in humans is associated with increased gut permeability related to bacterial overgrowth in the small bowel and disruption of intestinal mucosa intercellular tight junctions. In human, the association between the pathology of obesity and type 2 diabetes and the alteration of gut microbiota has been an interesting area of study.[121,135–139] Human studies have revealed that *Bifidobacterium* and *Faecalibacterium prausnitzii* abundance appears to be lower in overweight, obese or type 2 diabetic patients than in lean subjects.[138–140] Interestingly *Bifidobacterium* and *Faecalibacterium prausnitzii* are correlated with anti-inflammatory effects.[140,141] However, whether the alteration in gut microbiota observed in obesity and type 2 diabetes are a cause or a consequence of the pathology remain unknown.[142]

Neurodegenerative illness: The brain is strongly coupled with the gut via 200–600million neurons.[143] It has been suggested that the gut and the brain maintain a bidirectional communication which is facilitated through a number of ways including the autonomic and enteric nervous systems, the neuro-endocrine system and the immune system.[144] The notion of gut-brain axis first came forward from the field of GI endocrinology and the discovery of hormonal regulation of digestion.[145] Since then it has been found to be associated with safeguarding the homeostasis of several systems including GI function and weight control.[146] Therefore, it is reasonable to include the gut microbiota as an important contributor to this system and as a result the term "microbiota-gut-brain axis" has come up.[147,148] Currently a growing number of clinical data and experimental observations suggest the presence of bidirectional gut–brain axis - implying that there are probably many types of neuro-atypical symptoms; including stress, depression, anxiety, associated with the alteration of the normal composition of gut microbial flora.[149,150]

It has been reported that chronic depression is associated with a distorted microbial composition and colonic motility in mice.[151] Interestingly it has also been reported that chronic gastrointestinal inflammation can actually induce anxiety-like behavior and modify the central nervous system biochemistry.[147,152] External factors such as stress or depression influence the course of GI diseases such as irritable bowel syndrome and inflammatory bowel disease.[153] Furthermore, stress can alter the integrity of the GI epithelium modulate GI motility and induce the release of catecholamines and cortisol which has direct effect on intestinal immunity and cytokine production.[154] Bailey et al.[155] demonstrated that exposure to a social stressor affects the gut microbiota and circulating levels of cytokines particularly IL-6 and MCP-1. Indeed, social stress has been reported to an increasing possibility of inflammation-related diseases enhancing the inflammatory gene expression and monocytes differentiation.[156] One quite widely used model of early life stress is maternal separation in rodents. Several groups have reported that stress introduces long lasting hyperactivity of the HPA-axis,[157–163] anxiety-like behaviour,[161,164–168] visceral hypersensitivity[166,169–171] and altered cholinergic activity in the gut[172,173] accompanied by increased intestinal permeability.[163,172,174,175]

The Autism Spectrum Disorder (ASD) is a collection of neuro-developmental disorders characterized by obscurity in social interaction and communication in affected children. It is typically associated with limited repetitive and stereotypic behavior and is noticeable within the first 3years of life.[176,177] Until 1990 Autism was treated as a rare psychological disorder. Today it is a major health concern, big emotional burden for families and large financial burden for the government worldwide. Though the principal cause of this disorder is yet to be known; gastrointestinal disorders have frequently been reported in the children with autism- suggesting the probable link between the atypical compositions of human gut microbiome with ASD.[178] The hypothesis regarding the gut microbiota and ASD linkage was first coined by Bolte et al.[179] Their study showed that interruption in the normal composition of native gut flora resulted colonization of some neurotoxin producing bacteria, contributing to the autistic symptom. As the importance of gut microbiota in gut-brain function came emerging; probable role of diet, bacteria and enzyme became a field of important study in autism research.[180] It has been proved that there is a significant difference between the stool sample from autistic and normal children in terms of frequency of occurrence of four bacterial phyla specifically viz. *Firmicutes, Bacteroids, Actinobacteria* and *Proteobacteria*. Further studies have shown higher count and diversity of *Clostridia* (mainly *Clostridium tetani, Clostridium perfringens* and *Clostridium boltae*) and *Desulfovibrio* (mainly *D.sulfuricans, D.fairfieldensis* and *D.piger*) in fecal samples of children with autistic behavior as compared to the normal healthy children with same sex and age.[181–188] Evidence suggests that high occurrence of *Bifidobacterium* and *Lactobacillus* species is a biological indicator for healthy gut microbiota in breast-fed infants as they serve important probiotic function in the gut.[189–191] As expected

these organisms are frequently reported to be lower in patients with ASD. People are working with several animal models to investigate the expected link between gut microbiota and autism like disorders. One recent paper on maternal immune activation (MIA) mouse model has revealed gastrointestinal abnormalities and changes in the gut microbial community in offspring of MIA animals with autism-like symptoms.[192] One recent study demonstrated that the alteration in the concentrations of short-chain fatty acids in the fecal sample of children with ASD.[193] This suggests that atypical production of such microbial metabolites may have a direct effect on our brain function and thus bacteria can modulate the brain function in a straight line.

Conclusion

The gut microbiota influences host metabolism, immune functions and host homeostasis. Interruption in this balanced community may generate very serious health troubles for the host. However, we have to keep it in mind that the study on the gut microbiome effecting health and disease is still in its infancy. Why the 'good guys' in our body all conspire to act as 'bad guys' is a fascinating question. It is a matter of debate, is the diseased state basically the cause of the microbiota dysbiosis? Or is it the consequence of the alteration of gut microbiota in host body? I.e. whether the disease itself creates the microbiota dysbiosis or the altered microbiota creates the disease in the body. Advancement of next generation genomic technology will pave the way to the development of experimental models of representative examples from the human gut microbiome. This will consecutively accelerate the discovery, testing and validation of novel drug targets. Future metagenomic research is also expected to focus on the complex relationships of the gut microbiome composition and host metabolism so that in time their actual importance to human health will also be understood better. More in depth understanding of the specific relationships between the gut microbiota and disease will enlighten us about the potential therapeutic targets. The issue of intelligent modulation of the intestinal community is a topic of great interest nowadays. The gut microbiome is expected to contribute immensely to the delivery of personalized healthcare strategies that are already being applied into the clinical environment for the benefit of patients. It can open new door to treating disease and potential modulation of human disease risk factors.

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Conflict of interest

Author declares that there is no conflict of interest.

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