

## Diversity of Gut Microbiota Associating Human Diseases: A Review

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Received: December 14, 2017; Published: January 31, 2018

### Abstract

Gut microbiota is immensely diverse, harboring trillions of microbes in human intestine and varies among individuals with fluctuation especially during early development and disease conditions. These diverse microbiotas form a complex ecological community that has been shown to influence significantly the host's normal physiology and susceptibility to diseases by its metabolic activities and the interaction with the host and within themselves. Again, microbial dysbiosis is associated with several disorders in human, such as malnutrition, obesity, cancer autoimmune diseases and so on. Thus, understanding the reasons behind the diversity of both the composition and function of gut microbiota will lead to tailor therapies that target these diseases. In this study, we reviewed these reasons that influence the diversity of the gut microbial composition in individuals and the host-microbes interactions that is crucial to some extent to make the host susceptible to several diseases. By understanding these microbial diversity from an ecological perception would provide insight on ways how to uphold human health by targeting microbial community during clinical treatments.

**Keywords:** Gut Microbiota; Microbial Diversity; Dysbiosis; Human Health; Diseases

### Abbreviations

IBS: Irritable Bowel Syndrome; IBD: Inflammatory Bowel Disease; SCFA: Short Chain Fatty Acid; CRC: Colorectal Cancer

### Introduction

Humans provide a scaffold on which miscellaneous microbial ecosystems are established. Not only humans, but also all mammals go through a life-long process of colonization that starts instantly after birth, by extraneous microorganisms that occupy mostly on mouth, gut, vagina and skin [1,2]. These microbial association that inhabit in and on the body, collectively constitute the microbiota, and the genes they represent is communally called the microbiome. This complex community includes bacteria, viruses and archaeon that significantly impacting both the host's health and physiology by interacting with the host and with each other [3,4]. Both the humans and the other mammals sustain this one of the most multifarious microbial ecosystems from the beginning of the birth till the adulthood [5].

Due to the significant role of the microbiota in health and disease of human beings, they are so often called our 'forgotten organs' [6]. Symbiotic microorganisms of the mammalian gut have been appreciated as they offer benefits to the host: extracting nutrients and energy from the diet and store them, fermenting and absorbing undigested sugars [7] and a variety of metabolic functions as well, which performed as an strong influence to establish these bacteria as mammalian symbionts [8]. Perhaps even more significantly, gut microbiota cooperates the immune system by providing signals that endorse the maturation of blood cells and normal progression of immune functions [9], defend the colonization of opportunistic pathogens and cooperate in the intestinal architectural development [10].

Again, one of the biggest health problem is child malnutrition, worldwide, that cannot be attributed alone to food security [11]. Although, existing therapeutic approaches have condended mortality among the children, they have partial efficiency in amending long-term sequelae, particularly stunting, neurocognitive deficits and immune dysfunction. Current works are providing insights in disease pathogenesis about the effect of impaired development of gut microbiota [12]. Furthermore, disturbances in the normal balance between the host and the gut microbiota have been associated with obesity [13,14], neurological disorder [15], inflammatory bowel disease (IBD) [16,17], diabetes and cancer [18].

### Composition of the gut microbiota

Traditionally, the gut microbiota was considered to be composed of 400 - 500 species of microbes, but the modern advancement of molecular classification into operational taxonomic units (equivalent to species) revealed that there are more than 1000 OTUs are existing in the gut of each individual of different societies and with the increment of age, the diversity of OTUs increases [19]. *Firmicutes*, *Bacteroidetes* and *Proteobacteria* constitute the major phyla of gut microbiota while *Actinobacteria* par a minor fraction among the total microbiota in mammals. Bacteria belonging to phyla *Bacteroidetes*, *Firmicutes* and *Actinobacteria* (to a lesser extent) primarily influence the human metabolism and nutrition. *Bacteroidetes* include genus *Prevotella* and genus *Bacteroides* prominently while *Firmicutes* include *Faecalibacterium*, *Eubacterium*, *Ruminococcus* and *Roseburia*. The predominant genus belonging to *Actinobacteria* is *Bifidobacterium* in the human gut [20].

In the reviewed samples, *Firmicutes* and *Bacteroidetes* were predominant among the microbiota, with *Bacteroides* being most divergent and abundant. Three different enterotypes were identified based on bacterial abundance. In the three enterotypes, *Bacteroides*, *Prevotella*, and *Ruminococcus* were most abundant respectively. In enterotype 3, the archaeal genus, *Methanobrevibacter* was found to be plentiful suggesting that in determination of composition of enterotypes, availability of hydrogen disposal pathways might play an important role [21].

### Factors that drive microbial diversity

Having established the concept that the gut microbiota in healthy individuals is highly variable, the next is to understand the reasons behind its variations thus this information can be utilized to design new therapies and clinical trials. For instance, if members of a family contain similar microbes; it would determine that family history of microbiota-stricken disease is informative. When designing cohorts,

the extent to which microorganisms varies due to pregnancy or even age should be taken into account. Another approach for considering microbiome-linked diseases is to ascertain the sensitivity of the gut microbiota to the external factors: environment and diet.

### Age

The infant gut is supposed to be sterile in the uterus and exposed to microbes during the progression of birth or immediately thereafter [22,23]. It was hypothesized that the alteration to strict anaerobes from facultative anaerobes occurs in neonates after the first week of birth, but molecular studies confirm that the conversion occurs very rapidly [24,25]. Infants experience much more diversity both in microbial communities and in functional gene repertoires compared to adults. Nevertheless, microbiome of infants do share distinctive functional and compositional properties across individuals and population [19]. Two reasons that affect the infant microbiota are the process of delivery and the use of antibiotics. Not only the diversity of gut microbiota of early life affect their composition in adulthood but also compositional changes however linked with metabolic and inflammatory disorders, such as obesity, irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD) [26].

### Genetics and Environment

It is still unclear that how factors such as the genetics and environment figure the gut microbiota, partially these factors are often confounded. Mother-daughter pairs or twins have more similar microbiota configurations compared to unrelated individuals, indicating that there must be a genetic impact over the microbiota [27]. However, likewise microbiota is shown in monozygotic and dizygotic adult twins which provide the suggestion that environment may drive familial similarities rather than genetics [28]. According to the characteristic differences of gut microbiota, particular populations can be separated. For example, children of rural Africa have a different microbial population from Italian children [29], and both the children and adults Malawi and the Amazonas state of Venezuela have a different microbiota from the population of the United States [26].

Although genetically different, these populations could also differ due to the influence of other that could shape the microbiota, such as environmental exposures, cultural factors, adequate sanitation and standards of cleanliness [20,21].

In particular, how cultural traditions influence the microbiota should highlight the reasons that cause marked differences in the onset of diseases connected to microbiota. For example, the frequency of IBD and other allergies are much greater in industrialized Western societies compared to agrarian cultures [30]. To understand these associations, an expanded studies will require that includes a greater number of samples and the confounding factors should be controlled as well. This may come with the formation of a human microbiome diversity project that counterparts the Human Genome Diversity Project [31].

### Diet and Medicine

A significant approach to explain the deviation of gut metabolic processes among individuals is the differences in the microbiota and the microbiome [32,33]. Many of these metabolic processes are outside the usual functional core, thus they can motivate host-specific responses. For example, the health benefits of soya containing diets are improvements in osteoporosis, vasomotor symptoms, cardiovascular disease and prostate cancer, which have been attributed to (S)-equol production by bacteria from the soya isoflavone daidzein rather than by human enzymes [34]. On average, 50 - 60% of adult population from China, Japan or Korea produce (S)-equol from a soya-rich food while only 25 - 30% of adults in Western countries produce (S)-equol [35]. Thus the cancer-protective properties of soya beans are not as effective for the Western populations as for the Asian adults.

Similarly, the metabolism of widely used analgesic paracetamol to paracetamol sulphate or paracetamol glucuronide can be determined by the gut microbiota, potentially shifting its efficacy and toxicity. The microbes facilitate this metabolic phenotype by generating the compound p-cresol, which competes with paracetamol for human enzymes that catalyse sulphonation [32]. The difference in drug metabolism among the populations requires population-specific drug trials to examine the effectiveness and toxicity of drugs. This functional variation of microbiota according to individuals is an emerging component of personalized medicine that makes the drug therapy more specific [36].

### Dysbiosis and Diseases

#### Malnutrition

Malnutrition is a global health problem that is associated with numerous adverse outcomes, including immune dysfunction, persistent stunting, and neurocognitive deficits. Current approaches to deal with these long-term sequelae have only partial effects in recovery, suggesting that few features of host biology must not being sufficiently repaired. This promotes the hypothesis that health development is dependent, partly on normal postnatal gut microbial growth and the perturbations in its development (resulting immature microbiota) are causally responsible malnutrition [12]. Preclinical proof-of-concept (PoC) that immature gut microbiota is a contributing cause rather than simply an effect of malnutrition has come from the experimental trail of Laura, *et al.* They transplanted gut microbiota from

both the healthy and undernourished Malawian children to Gnotobiotic mice. Unlike mature microbiota from healthy children, immature microbiota from the undernourished resulted diminished growth, metabolic abnormalities in brain, muscle and liver and altered bone morphology as well to the recipient Gnotobiotic mice. Again, the effect of age-discriminatory taxa on the recipient Gnotobiotic mice was also correlated and remarkably, the body mass was found to be significantly greater when 6-month-old microbiota were transplanted compared with the 18-month-old microbiota. Thus the hypothesis developed that both the growth and age-discriminatory taxa of gut microbiota would help to recover or prevent the malnutrition and would be a potential therapeutic target [37].

### Obesity

Several studies indicated that characteristic alterations in gut microbiota configuration is associated with obesity. It is found that gut microbiota in obese mice lack the leptin gene, indicated that there was a remarkable significance of the phylum Firmicutes compared with Bacteroidetes [38]. This was resulting in increased expression of enzyme coding genes responsible for carbohydrate breakdown and SCFA metabolism [39]. Thus, those mice had higher SCFA concentration in their feces and reduced fecal energy losses compared to the conventional mice. This proposed that the obese mice used their dietary carbohydrate as a significant energy source that ultimately led to the obesity. Further investigation showed that Gnotobiotic mice developed obesity when they were transformed with the gut microbiota from the obese mice, reflecting significant contribution of microbiota in the development of obesity and energy consumption. Expectantly, human association studies in various parts of the world revealed that the gut microbial composition of obese people show alterations compared with lean individuals [40,41].

### Type 2 diabetes

Type 2 diabetes is associated with compositional changes in the intestinal microbiota mostly apparent at phylum and class levels. The relative abundance of the phylum *Firmicutes* was found to be significantly lower, while the percentage of the phylum *Bacteroidetes* and *Proteobacteria* were much greater in diabetic patients compared to the non-diabetic counterparts. Accordingly, the ratios of *Bacteroidetes* to *Firmicutes* are positively and significantly correlated with abridged glucose tolerance [42].

Bacteroides-Prevotella group versus class *Clostridia* and *C. coccoides* - *E. rectale* are the bacterial groups that distinguish the diabetes from the non-diabetic patients. Again previous studies showed that the decrease of inflammation and metabolic endotoxin is associated with the reduction in *Bacteroides-Prevotella* spp. [43]. Accordingly, a significant increase in the *Bacteroides-Prevotella* group and a decrease in *Clostridium* spp. *C. coccoides* along with lean body weight have been detected in human studies [44]. Again, the significantly higher levels of the *Lactobacillus* and *Bacilli* group in diabetic subjects in mice models compared to controls in a study have been reported in relation to type 2 diabetes and to obesity as well [45].

### Autoimmune Disorders

Further evidence on the correlation between the microbiota and autoimmune disease led the significance of gut microbiota in typical immune function. It has been shown that the interaction of innate immune system with the gut microbiota modifies predisposition towards developing type 1 diabetes in mice [46]. Children at higher genetic risk for type 1 diabetes exhibit a distinct configuration of gut microbiota compared with non-autoimmune individuals, with reduced diversity over time and increased relative abundance of *Bacteroides ovatus* and firmicute strain CO19 [47]. Again results in animal models suggest a significant influence of the gut microbiota on rheumatoid arthritis and multiple sclerosis and these autoimmune diseases do not develop in gnotobiotic mice. The disease phenotype is regained when gnotobiotic mice are transformed with specific bacterial taxa [48].

### Crohn's Disease

Intestinal mucosal inflammation and related environmental factors might be a cause of Crohn's disease which is known to be a chronic gastrointestinal disorder [49,50]. There was a surprising study of Cadwell, et al. that virome, genome, and microbiota might play an interacting role in the initiation and development of Crohn's disease. Cadwell, et al. studied mouse lines which had a hypomorphic (HM) Atg16L1 gene [51]. In this study, Cadwell, et al. used mouse lines with a hypomorphic (HM) Atg16L1 gene, which was known to have a link with developing Crohn's disease [52,53]. It was previously identified that epithelial and Paneth cells have association with mucosal immunity. When Atg16L1HM mice were infected with murine norovirus, Paneth cells exhibited abnormalities but wild type did not show any changes. This occurrence led to the hypothesis that the amalgamation of a virus and a susceptible gene might have resulted in Paneth cell abnormalities [54]. Thus, not only the gut microbiota but also combination of virome and host genetic composition play a significant role in pathophysiology of this disease [46].

## Cancer

With the upsurge of colorectal cancer (CRC) patients, more studies are now being focused on association of gut microbiota with the development of this disease. However, whether gut microbiota or diet alterations or any physiological change is the underlying reason is difficult to determine as CRC tends to develop over many years. In order to differentiate causal agent for CRC and those respond to disease onset, a 'driver-passenger' model for CRC was proposed in an article [15]. Fecal sample from CRC patients were collected and 16S ribosomal RNA gene sequencing analysis revealed that *Bacteroides fragilis* and several enterobacterial operational taxonomic units (OTUs) were observed to be increased when compared with normal healthy people. However, five OTUs that correspond to butyrate-producing Lachnospiraceae were significantly decreased [55]. Again, changes were observed in tumor associated microbiota with an increase in *Fusobacterium* spp. *Leptotrichia* spp. and *Campylobacter* spp. can co-occur with *Fusobacterium* spp. analysis revealed by Deep metatranscriptomic sequencing [56,57]. After treating mice with carcinogenic agents to induce tumor, the composition of gut microbiota was observed. *Odoribacter* spp. *Akkermansia* spp. and *Bacteroides* spp. were found to be increased, whereas *Porphyromonas* spp. and *Prevotella* spp. decreased [58]. The emergence of potential carcinogenic bacteria leads to the notion that not a single organism, but a group of bacteria can drive the process of tumorigenesis [59].

## Future Perspectives

We have already known that disparities in the gut microbiota can lead to health complications. Though each person's microbiota has some resistance to perturbations, it can be overcome by probiotics, diet, and drugs; analysis revealed by high-throughput sequencing. However, there are success stories like transplantation of a foreign gut microbiota can be a good treatment option for bringing back a healthy microbial community [60].

Thus, transplantation experiments led to the idea that changing microbial community can be a striking force in disease development. Genetic influences that affect disease phenotypes can also cause dysbiosis in the gut. Taking the microbiota from the diseased and by inoculating it in the germ-free wild-type hosts; phenotypes can be transferred [61,62]. Another study where the microbial community was transplanted from a healthy donor to a *Clostridium difficile* associated disease (CDAD) patient considerably modified the bacterial composition in the patient; led to the belief that, transplantation from a healthy to a diseased individual can benefit in improving gut microbial balance [63]. Surprisingly after 14 days, the microbiota of the recipient was found to be changed extensively from a Firmicutes- and *Bacteroidetes*-deficient state to a community which is dominated by *Bacteroides* spp. that is similar to the donor. Not only this dramatic change in composition of microbiota occurred, but also symptoms associated with CDAD patients also disappeared [46].

## Conclusion

In summary, the findings we reviewed propose that, to gain an advancement on our health and disease, we are in need of an improved characterization of gut microbiota, including the way its diversity provides different functional profiles. Besides, an integrated study should also be taken account that insight on the interaction between the host, the microbiota and the environment. An emerging variety of disorders, several diseases and even behavioral problems are being found to be correlated with the host microbiota [64,65]. Ultimately, the large-scale sequencing projects, such as Earth Microbiome Project and the Human Microbiome Project will provide an all-encompassing view to understand the relationship between microbiota and health.

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**Volume 14 Issue 2 February 2018**

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