An overview of normal human gut microbiota and dysbiosis

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Abstract

In modern science, "gut health" is becoming very popular for its success in various therapeutic aspects. Human gut microbiota starts to colonize during birth, grows in parallel with host, and develops at 3-5 years of age like an adult. Ecological and evolutionary pressure determined the composition and diversity of gut microbiota. However, gut microbiota depends on an individual's ethnicity, diet, lifestyle and health conditions. It may vary from person to person and from population to population. The established gut microbiota plays an important role in the protective, metabolic and structural landscape. Disturbance of ecological balance, known as "dysbiosis" linked with unhealthy diet, antibiotic uses, stress, etc., may profoundly influence various diseases. Research on gut microbiota explores exciting developments in therapeutics, such as prebiotics, probiotics, drugs and fecal transplantation for improved health.

Keywords: Gut microbiota, Health, Dysbiosis, Therapeutics.

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Introduction

The human microbiota represents an assemblage of microorganisms (bacteria, archaea, protists, fungi and viruses) on and within body that includes skin, mouth, gut, vagina, etc. The collective genome of all microorganisms is called 'human microbiome', which may vary from person to person.[1] In the year 2001, the human genome project was completed and reported approximately 22,300 genes of human genome. After the project's completion, it was argued that the "crowning achievement" in biology would be incomplete until the synergistic activities between human and microbes are understood. In 2005, a high-throughput sequencing technique (next generation of sequencing called NGS) was developed to overcome the difficulties identified in Sanger's method in terms of ease, cost and time. Subsequently, several projects were initiated worldwide to understand the relationships between human and human-associated microbial communities.[2,3] Discoveries of the Human Microbiome Project (HMP), the Metagenome of Human Intestinal Tract (MetaHIT), the Australian Gut Project, the American Gut project, the British gut project, the Canadian Microbiome Initiative, the Human MetaGenome Consortium Japan, the My NewGut project of the European Union and the International Human Microbiome Consortia, etc. opened new horizons for a better understanding of the complex gut ecosystem and its role in health and diseases. In 2010, catalogues of 3.3 million non-redundant fecal microbial genes were reported using NGS.[3,4] The number of genes was 200 times more of human genes than any previous studies reported. Apart from different colonization sites of the human body, the gut (~ 200-300 square meters of mucosa) is the "secret garden" of 100 trillion diverse microbes, mostly bacteria. The number of microbes is ten times more than our somatic and germline cells and weigh up to 2 kg. In an individual 150 to 170 bacterial species predominate and enjoy the warm and nutrient-rich environment of the gut.

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In early life, the microbiota plays an important role in the development of our innate and adaptive immune systems. Once homeostasis is established, it forms a firewall and protects the body from outsiders. The normal microbiota plays an important role in our body's immunological, metabolic and structural landscapes.[5,6] Experimental base evidence explored a range of diseases and disorders linked to the altered microbiota profiles, a state called 'dysbiosis'. Dysbiosis is defined as an "imbalance" in the gut microbial community due to the gain or loss of community members or changes in relative abundance. A growing list of disorders and diseases have been associated with gut microbial dysbiosis such as Crohn's disease, ulcerative colitis, inflammatory bowel syndrome, obesity, type 2 diabetes, autism, Parkinson's disease, Alzheimer's disease, multiple sclerosis, lupus, rheumatoid arthritis etc.[7] In the recent review functions and overall dysbiosis of gut microbiota are summarized.

Distinctly of gut microbiota

Microbial diversity on our planet is vast: 55 divisions (deep evolutionary lineages) of Bacteria and 13 divisions of Archaea

have been described to date and much diversity remains unexplored. Apart from different microbial colonization sites, gut is the most stable and enriched ecosystem consisting of diverse bacteria. The relationship between gut microbiota and humans is commensal (one partner benefits while the other seems unaffected) rather than mutualistic (both partners benefit). This relationship is an outcome of ecological and evolutionary selection. Host-level selection "top-down" selected the microbial community with a high degree of functional redundancy. An opposing selection pressure originated from the microbes known as "bottom-up" to become functionally more specialized to contribute to the host. These selective pressure allowed only seven predominant divisions of bacteria (Firmicutes, Bacteroidetes, Actinobacteria, Fusobacteria, Proteobacteria, Verrucomicrobia and Cyanobacteria) to adhere on gut wall.[8] Among these seven divisions, the Bacteroidetes and Firmicutes constitute more than 90% of the total population. However, the diversity and functionalities of gut microbiota may depend on ethnicity, culture, diet and geographical location. Worldwide data classified the gut microbiome based on functionalities into three types of called 'enterotypes', i.e. Bacteroides, Prevotella, and Ruminococcus.[9] Overall, human beings possess any of the three types of Enterotypes strongly associated with long-term diets. The protein and animal fat diet favours the "Bacteroides" eneterotype, whereas the plant and carbohydrate base diet establishes the "Prevotella" enterotype. The "Ruminococcus" enterotype is associated with long-term fruit and vegetable consumption.

Changes of the gut microbiota and age

Microbiota is acquired at birth and develops in parallel with the host. Previously, it was thought that the womb, placenta, amniotic fluid and meconium are sterile and microbiota starts to be acquired after birth. However, a group of researchers detected the microbes in the placenta, amniotic fluid and meconium by PCR and DNA sequencing-based methods and hypothesized that horizontal transfer of bacterial DNA from mother to fetus happened via the placenta. So, there is controversy over two opposing hypotheses "sterile womb" vs "in utero colonization". [10]Apart from controversies, a number of studies showed that hormonal changes in healthy pregnancy alter the vaginal microenvironment. As a consequence, vaginal microbiome alter significantly, including a decrease in overall diversity, increased stability, and enrichment with Lactobacillus spp. During vaginal delivery, gut microbiota of infant acquired microbes from vagina including *Prevotella, Sneathia*, and *Lactobacillus* spp. In contrast, c-section (Cesarean delivery) infants acquired microbes from mothers' or nurses' and clinicians' skin surface dominated by *Propionibacterium, Corynebacterium,* and *Staphylococcus* spp.[11] After birth, breast and formula feeding determine gut microbiota composition. Breastfed infants consume more lysozyme, immunoglobins, lactoferrin, and complex polysaccharides like glycans, sialylated and oligosaccharides. Consumption of mothers' milk encourages the growth of good gut microbiota like *Bifidobacterium sp*, *Bacteroides sp*., and *Lactobacilli sp*., whereas, formula fed encourage the growth of *Clostridium, Granulicatella, Citrobacter, Enterobacter* and *Bilophila*.[12] Research base evidences showed that vaginal birth and breast-fed infant acquire healthier gut microbes as compared to the formula-fed infants. At the age of 3 to 5 years, microbiota's unstable structure and composition starts to differentiate and acquires similarity (40–60%) to that of adult. During this period, the gut microbiome also changes in parallel from the earliest lactate utilization to plant polysaccharide digestion, vitamin biosynthesis and xenobiotic degradation. The composition and functions of the established microbiota remain same if there is no change in long-term dietary habits, antibiotics treatment, stress and pathophysiology in adulthood.[3,12]

Functional aspects of gut flora

The gut microbiota performs essential functions in gut, including protective, structural, and metabolic (Figure 1).

Metabolic function

The gut microbiota digests the undigested foods, derives energy and produces vitamins, amino acids, short chain fatty acids etc. Importantly, the microbiome ferments non-digestible fibre and endogenous mucus. The major metabolites produced by fermentation are short-chain fatty acids (SCFAs). Major SCFAs are acetate, butyrate, and propionate, which are involved in the modulation of immune system and provide energy to colon epithelial cells. Apart from serving as an energy source, butyrate also regulates energy homeostasis by stimulating gut enteroendocrine cells to produce leptin from adipocytes, including Glucagon-like peptide-1 in L cells. Acetate is the principal short-chain fatty acid serves as a primary substrate for cholesterol synthesis, whereas, propionate have shown to reduce cholesterol levels *in vivo*. Clinical trials have yet to be confirmed these observations. Therefore, the gut microbiota's metabolic activities are multifunctional and essential for host metabolism.[13]

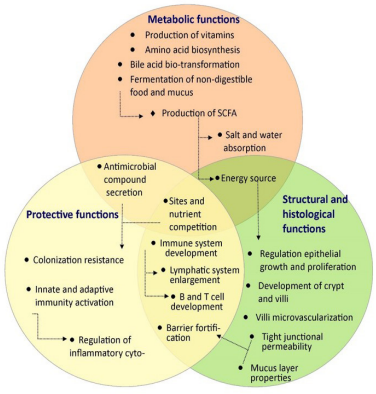

Figure 1: Main beneficial functions of the human gut microbiota. Circles represent the three principal classes of functions performed by the bacteria that inhabit the gut. Arrows represent causal relationships. SCFA, short chain fatty acid.

Protective function

Pathogen displacement or "colonization resistance" is prime functions of the gut microbiota. Gut microbiota prevent pathogenic colonization by competing the sites for attachment and nutrients. Experiments in Germ-free mice showed an underdeveloped lymphatic system, with fewer Peyer's patches and lymphoid follicles and more prone to infection. Signals from intestinal bacteria help in development of both innate and adaptive immunity to maintain proinflammatory and anti-inflammatory response.[14,15] Apart from indigenous gut microbiota, microbial-associated component also stimulate immune response. For example, capsular polysaccharide A, produced by *Bacteroides fragilis* showed an anti-inflammatory effect in gut. Microbial metabolites like butyrate exert immunomodulatory effects by suppressing nuclear factor-kb activation and/or by acting on G-coupled receptor. Therefore, the commensal microbiota of the gut play active roles in the development and homeostasis of immune responses.[14]

Structural function

The microbiota fortifies the barrier function of the gut. Metabolic end products of gut microbiota (e.g. SCFA) provides energy to colonic epithelial cells that regulate the growth and proliferation of colonic epithelial cells, development of crypt and villi and microvascularization. The intestinal epithelium is a single layer of columnar cells that are tightly bound together by intercellular junctional complexes that regulate paracellular permeability.[16] The junctional complexes consist of tight junction (ZO; zonula occludens), adherens junction (zonula adherens) and desmosome. The adherens junctions are located beneath the tight junction and both make the apical junctional complexes associated with actin cytoskeleton. Gut microbial metabolites help reinforce the tight junction that prevents the influx of bacterial endotoxins (LPS) into the systemic circulation.[17] Gut microbiota also determine the secretion of mucin i.e. acidic of basic to prevent pathogenic infection.

Dysbiosis of gut microflora

The intestinal "dysbiosis" hypothesis evolved from the bowel "toxaemia theory" coined by the Nobel laureate Elie Metchnikoff. These theories highlighted that disturbance of microbial ecology in gut showed harmful effects in host via: (1) Increase of pathobiont, (2) Loss of bacterial diversity, and (3) decrease of good gut bacteria (Figure 2). Alterations in bacterial metabolites and the overgrowth of pathogenic microorganisms result in the release of toxins that play a role in chronic and degenerative diseases.[18] In dysbiotic state the permeability of gut is altered, which can cause influx of endotoxins into systemic that induces chronic inflammation in the different body organs. The mucosa exposed to bacterial products-endotoxins, hydrogen sulphide, phenols, ammonia, and indoles-that can harm mucosal and host health. The presence of many of these toxic metabolites is

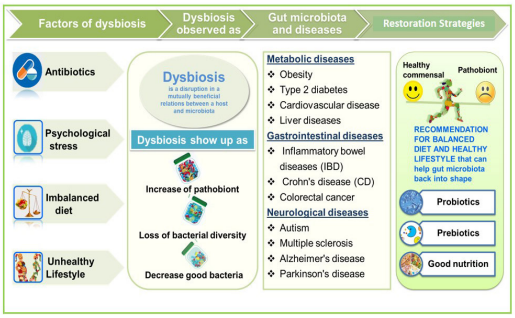

Figure 2: An overview of dysbiosis of gut microbiota in different diseases and restoration strategies in various diseases

directly dependent on the type of bacteria and fermentation process. In turn, fermented products have the capability to regulate immune homeostasis and structural functions. Diets high in protein and sulfate have been shown to contribute greatly to producing these potentially toxic products. The production and absorption of toxic metabolites is referred to as bowel toxemia.[19] Many factors can alter the gastrointestinal ecosystem, including antibiotics, psychological and physical stresses, radiation, and dietary changes (Figure 2). Currently, the focus is on describing dysbiosis in a plethora of human disorders. Research evidence showed that dysbiosis of gut microbiota is linked with metabolic diseases like diabetes, obesity, cardiovascular diseases and liver diseases.[20] Thus, the knowledge of the factors that can cause detrimental effect of the microbiome is becoming increasingly important to researchers. Gastrointestinal diseases like inflammatory bowel disease, Crohn's disease and colorectal cancer also associated with gut microbial dysbiosis. Neurological diseases like autism, Multiple sclerosis, Alzheimer's and Parkinson's disease linked with dysbiosis of gut microbiota.[20, 21, 22]

Future application of gut micobiota

It has now been widely agreed that microbiome exerts significant influence on both physical and mental health of an individual. In depth understanding of functioning of microbiome is necessary to formulate a strategy for targeted manipulation as and when required. With increasing economic development coupled with the modern lifestyle, there has been growing cases of diseases like hypertension, diabetes mellitus, dyslipidemia, obesity etc. which are the major risk factors for mortality and morbidity. Besides, the microbiome can also influence the efficacy of drugs used in diseases. Antibiotics may transiently cause dysbiosis in the gut microbiota and the spread of antibiotic-resistance genes in the gut, which may lead to difficulties in the management of gastrointestinal problems. Recent developments in the field has led to a new regime of next-generation probiotics that target a particular disease, fecal transplantation, prebiotics and probiotics personalized diet etc. to manage certain diseases. Other promising developments include controlling children's malnutrition, healthy aging, behavioral transplant, etc.

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Conflict of Interest

The authors declare no competing financial interests.

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