Review Article

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Multi-Potential Influence of Gut Microbiota on Human Health

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Abstract

It is not surprising than an adult human body contains hundred trillion bacteria. The composite microbial genome found in the mammalian gastrointestinal tract is termed as gut microbiome. Various metagenomic studies have tried to dissect out the distribution of microbiota in gut and the diversity of microbiome functionally related to the health conditions. Also these microbiomes are risk factors for illness such as asthma, inflammatory bowel disease and metabolic disorders. Human health is regulated by gut microbiome in many different ways, such as direct stimulation of afferent neurons of the enteric nervous system via vagus nerve to central nervous system inflammation, protection against infection, generation of innate memory and functional reprogramming of bone marrow progenitors. In this review article, authors discussed how the varying composition of gut microbiota at different situations related directly or indirectly to human health.

Keyword: Gut microbiota; Bioreactor; Gastrointestinal tract (GI tract); Innate immunity.

Introduction

Year 2002 is the year of microbiology, after discovery of full sequencing of microbial genes and microbial diversity was assessed to species level with inter individual variations at genus.[1] 60% of the weight of total of human stool is live plus dead bacteria. Till 2004, there was no clear recommendation that bacteria in the human gut could be a factor of controlling multiple function of body along with mental health[2] and then new field of research started with the study of the gut brain connection. Bacteria in the gut are BIOREACTOR, that process food. Being a bioreactor system, human gut requires regular feeding with a basic nutritional diet which can ensure the prime performance and regulate human health[3] and developing health management system depends upon the identical clinical evaluation of gut micribiome. Large numbers of metagenomic studies are initiated for the trasnslational research. But validations of independent data still need to be correlated with host quality of life with corresponding functional physiological functional outcomes. Such kind of data obtained by Valles CM et al., which provides a link of microbiome in human gut with that of mental health and their results showed the faecal metagenomes identified the microbial synthesis potential of the dopamine metabolite 3,4 dihydroxyphenylacetic acid as correlating positively with mental quality of life and indicated a potential role of microbial γ-aminobutyric acid production in depression.[4] Jeroen Raes says "The relationship between gut microbial metabolism and mental health is a controversial topic in microbiome research". In reality most of the bidirectional research study between gut microbiota and brain communication has been explored in animal models and human research yet to be confirmed. A study from young rat pups suggested that

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when pups were separated from their mothers, the stress early in the life could lead to long term changes in their life.[5] Later it has been reported that stressbehaviours of animals decreased and their brain chemistry changed when probiotic bacterium given to mouse,[6] however mice with severed vagus nerve did not get the same benefits. In 2018, Elaine Hsiao's discovery has the potential to impact on the research showing that GABA acts like a sort of brake for brain cells by which it reduces the activity in neuronal networks in properly balanced way and most importantly that GABA was provided by the gut microbiome.[7] May be not in the term, but the original theory similar to modern concept which indicates microbiomes are helpful and they give healthy and endurance of life.

Classification of Gut Microbiota

At all the surfaces of mucosa and barrier, trillions of microorganisms such as bacteria, fungi, viruses, archaea, protists and multicellular eurkaryotes are constitutively colonized and collectively referred as microbiota. The greatest diversity of microbes present in the gastrointestinal tract. Healthy human harbour over 1014 bacterial cells and represents hundered of species, which encode 150 times more genes than the human genome.[8] In human gut, four common dominant bacterial phyla are Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria. Most bacteria belong to the genera Bacteroides, Clostridium, Faecalibacterium, Eubacterium, Ruminococcus, Peptococcus, Peptostreptococcus, and Bifidobacterium. The traditional setting for classifications and phylogenetic tree are based upon the morphological and phenotypic nature as shown in fig. 2.[9] However recent scientific community is more interested primarily identified by their molecular sequences because such molecular identification is much more straight forward to do in high throughput than morphological or phenotypic characterization. Considering the "omics" based approaches, the functional classification of microbiota are of two types (i) metagenomics classifications which is based on gene contents or gene sequencing or simply reveals "who is there," (ii) metabolomics classifications based on metabolic functions or system level functions or simply reveal "what they are doing". Classification of microbiota based upon whole-genome sequencing is going to have a profound impact on clinical research and practice and epidemiological studies.[10]

Origin of Gut Microbiota

Revolutionised medicine tries to understand the hidden bacteria inside the wall of digestive system. The Microbiota present in gut is not homogenous throughout and microbial composition varies along the GI tract. There occurs a great diversity among different age group as well as in different geographical regions. Several biopsy reports from healthy individuals were analysed and report shows that at different sites of the intestine different bacterial groups are enriched and form colony.[11] The question comes, from where these bacteria come and how they enter into GI tract. The source is from mother, food, environmental niche or skin niche. Immediately at birth, colonization of the human gut with microbes begins and it passes through birth canal and show similarity with mothers. [12] The microbial composition after 1 year of age starts developing and shaping the compositions of microbiota.[13] After the initial establishment, the microbiome of individual person relatively simple and varies widely between individuals with time.[14,15] Research data from mouse studies are performed in highly controlled environments, where exposure to microbes from sources other than littermates and parents is limited. Hence, large amount of investigations are needed to establish the role of parental inoculations in determining the gut microbiota composition of next generation.

Feasting and fasting

Ours feasting diet consists of mainly carbohydrate, Protein and fat. These foods have wide influence on the composition of the gut microbiome[16] and acute changes in diet alters the microbial niche within just 24 hours and reverse back to base line by 48 hours.[17] High-fat or high-sugar diets are more prone to circadian rhythm disruption[18] and anaerobic microflora along with bactiroids number enhanced by fat reach diet.[19] Distal part of the gut support to host health through biosynthesis of vitamins and essential amino acid and effects of microbiota on toll-like receptors (TLR) promotes the local intestinal immunity.[20]

Our digestive tract is the sanctuary of microbes. Inside our body trillions of microbes flourishing in different shapes and sizes and inhabit various parts of your body, particularly in gut. The majority of the gut microbiota is composed of anaerobes and their number increases while moving from proximal towards distal of GI tract[21] (shown in fig 1). These colonies of microbes get their feed, what we eat. Based on what we give our gut bugs, they can do digest and metabolize food and can convey the message to our brain when we feel full or hungry. In alteration, there is significant impact when we give ether no food, too much of food or too much food at the wrong times of day.

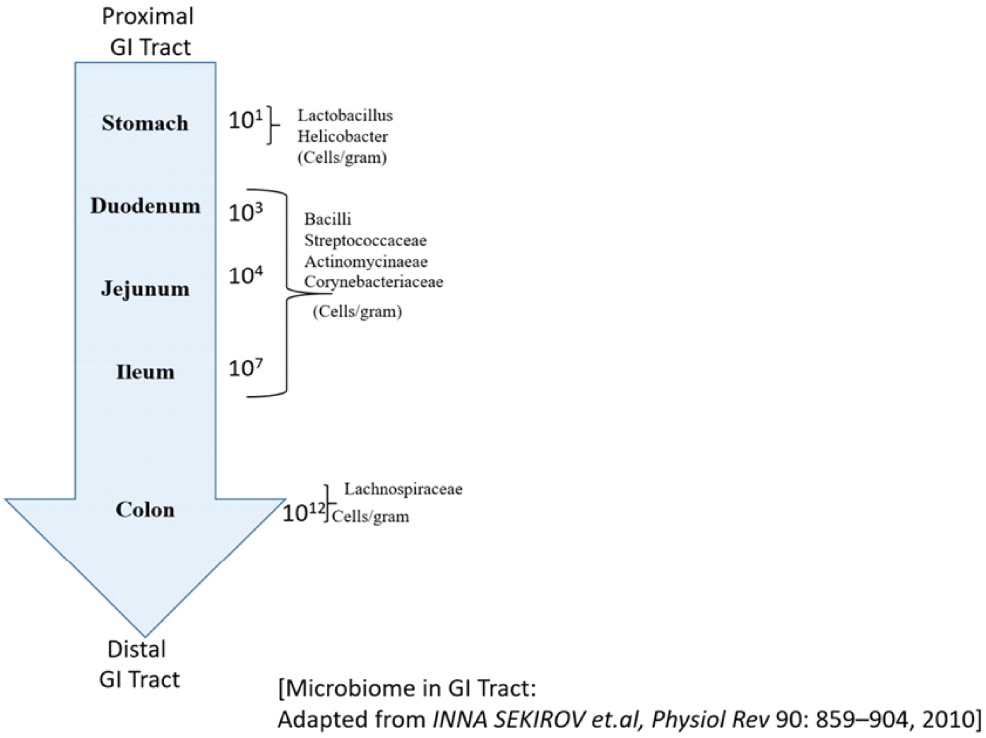

Fig. 1: Microbiome in GI Tract

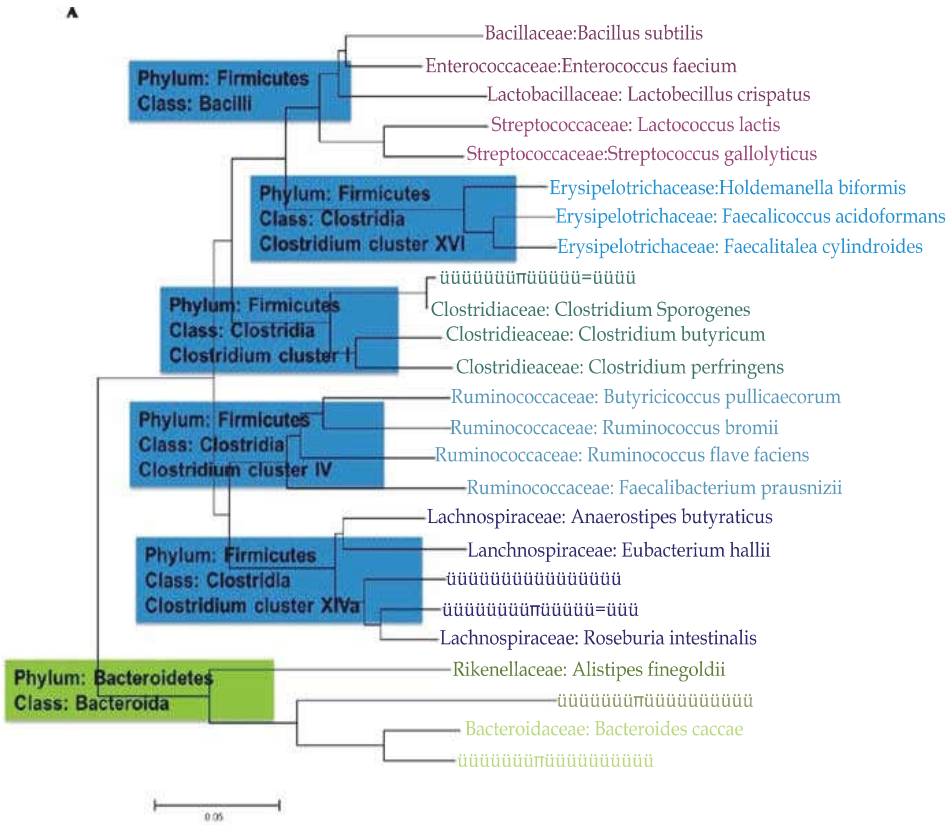

Fig. 2: Phylogenic classification of microbiota: Adapted from: Thesis on "Improving broiler gut health by prebiotic stimulation of butyrate-producing bacteria" submitted by Celine De Maesschalck, Ghent University, January 2015

Also intermittent fasting may have an impact too. Hence it is essential to consider our health of gut which in turn takes care of us to next level. Large number of study and systematic review in medical journal report that overweight obese adults follow weight loss diet. Those diets can be categorised into low carbohydrate, low fat and moderate macronutrient. The question arises whether losing weight and losing the gut microbiota happens side by side. Several recent studies using preclinical model demonstrate that bacteria when ingested in adequate amounts positive mental activity have been reported through the alteration of electrical activity.[22] Effects of fasting have been studied by various researcher and reports show the beneficial effect of metabolic markers.[23] In fasting, altered functions of gut microbiota indicate that (i) transition of white adipose tissue to brown adipose tissue occurs, which is a beneficial reaction (ii) increased level of acetate and lactate (iii) upregulation of monocarboxylate transporter in various tissues such as beige adipose cells, hepatic steatosis, insulin resistance and ameliorates obesity.[23] Time restricted feeding or intermediate fasting is an eating pattern which involves "feeding window" and "fasting window". During fasting period, gut microorganisms change the host physiology and number of functions in body. Gut microbiota helps in supply of alternative energy sources, such as ketone bodies[24] and various research studes in other animals supports the data.[25]

Function of Microbiota

In 1885, Louis Pasteur speculates that animals lacking bacteria in their gut would die.We realize the truth. Consequences of food what we eat has many different functions depending upon the type of food we eat. Metabolic health is regulated by diversities of microbiome.[26,27] and circardian rhythm is entertained by the food signals.[28] During healthy state, body's immune system reacts with pathomicrobes while tolerant for beneficial microbiota and that beneficial microbiota are called "Symbiont".[29,30] At the same time, many other species of bacteria are viewed as opportunistic pathogens or pathobionts and the immune system of our body carefully monitor the flora communities of our gut to maintain the host defence.[31,32] Microbiota of gut regulates the T cell homeostasis and their differentiation.[33] Microbes of gut interact with immune cells and induce them to secrete cytokines that circulate through the blood and reach at brain. Lipopolysaccharides provide low-grade tonic stimulation to the innate immunity through bacteria dysbiosis. Gut microbiota interacts with enteroendocrine cells and produce neuroactive peptides that sends signal to brain.[34] Gut microbes shape the architecture of sleep and stress reactivity of the hypothalamic pituitary adrenal axis. They influence memory, mood, and cognition and are clinically and the rapeutically relevant to a range of disorders, including alcoholism, chronic fatigue syndrome, fibromyalgia, and restless legs syndrome. In the immune cell development and function, gut microbiota plays a crucial role.[35, 36] Recent findings showed that the presence of previously encountred memories present in the non-immune cells of the hosts where the key players are host and gut microbe.[37,38] Gut microbes performs a great role in host the innate immune. Pattern recognitionreceptors (PRRs), expressed by innate immune cells such asdendritic cells (DCs), monocytes/macrophages, and naturalkiller (NK) cell which are key regulators and act as sensor for host microbe communications.[39-42] Gut Microbes are the intersection of diet and health. For survival of trillions of microbes reside inside the gut, dietary nutrients are essential. Hence to promote the metabolic health, mental health and immunological health, it is important to monitor the gut microbiota.

Gut Microbiota Regulate Innate Immunity

Innate immunity and its memory are involved with myeloid cells such as dendritic cells, monocytes and macrophages, innate lymphoid cells including natural killer cells, and bone marrow progenitor cells.[43] The microbiota derived ligands, products and any metabolic intermediate products initiates and affect the innate immune cells through the PPR. Pattern recognition receptors (PPRs) are the key molecular players that communicate the host and microbes.The training of PPRs expressing innate cells of microbiomeare prerequisite of protective innate immunity mechanism during secondary exposure/infection of pathogens.[44]

Role of Microbiota in Drug Metabolism

In comparison to overall microbial community, the gut microbiota contains a relatively active subgroup. There is remarkable variation in the proportion of physiologically active group of microbiota in healthy individual with that of unhealthy individuals those who takes drugs. Gut microbiome not only altered physiologically by short term exposer of drugs or xenobiotics, but also composition of overall microbiota and gene expression get altered significantly. These responses of change in gut microbiota and the molecular pathway involved in the xenobiotic metabolism and

the resting potential damage from the signalling molecules.[45] The human gut is an ecosystem harbouring diversified microbiota, productive bacterial community, shows a surprizing level of temporal variations with temperature, pH, nutrient variety and antibiotics. Also it seems the molecular pathways are inter related with the change of phage exposure, bile acids, host immunity and other ill-defined factors.[46]

Future Prospective

Many gut microbiota identified as probiotics and those were originally isolated from the gastrointestinal tract, and they were defined by the Food and Agriculture Organization of the United Nations (FAO)/WHO as "live Microorganisms. These probiotics are administered in adequate amounts confer a health benefit on the host. However systematic study and mechanism need to be clearly defined how these gut microbiota exert their beneficial effects on the host through (i) interference with potential pathogens (ii) improvement of barrier function (iii) immunomodulation (iv)production of neurotransmitters and (v) memory induction.An important clinical and scientific question is whether adopting a regular, intermittent fasting regimen is a feasible and sustainable population based strategy for promoting gut microbiota and metabolic health. The future clinical research should answer these questions.

Conclusion

Convenient amount of evident demonstrate that there is a very intimate relationship of host and gut microbiota. Several studies using preclinical data shows that microbiota involves in multifactorial function and it is highly reasonable. Supporting clinical finding are awaited.

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