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Review article

Update on the human microbiome and its clinical importance

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ABSTRACT

Background: The human microbiota is all microorganisms that live on and in humans as gut microbiota, vaginal microbiota, skin microbiota and so. The human microbiome consists of the human microbiota and the genes these cells harbor. The human microbiome is characterized by the huge number and wide diversity. The multi-omic approaches, including phylogenetic marker-based microbiome profiling, shotgun metagenomics, metatranscriptomics, metaproteomics, and metabolomics, have enabled the efficient characterization of microbial communities. The human microbiome produces a high amount of metabolites that can affect its host to the degree some scientists have considered it especially the gut microbiome as an extraorgan. The human microbiome accomplishes many vital processes. It maintains intestinal integrity and supports its barrier function. It provides essential nutrients like vitamin K and vitamin B. The human microbiome is vital to the innate and adaptive immune system. Disturbance of human microbiome can lead to somatic diseases as autoimmune diseases, obesity, metabolic syndrome, DM type II, and the development of cancer. Besides, the somatic disorders, dysbiosis was associated with autism and psychiatric disorders. This review article aims to shed light on updates on human microbiomes and its importance to human health. It will discuss the relation of dysbiosis to human diseases.

Introduction

The Human Genome Project (HGP), was an international research project to determine the base sequence of the whole human DNA and to identify and map the genes of the human genome. It was completed on April 14, 2003 [1]. The question is that, is the human body contains DNA only of the human genome? Certainly, the human body also contains the DNA of the normal microbial flora that inhabit the human body and its orifices [2].

The human microbiota is the new term used for normal microbial flora which are the whole members of microorganisms that live on and in humans. The human microbiome consists of the microbiota and the genes these cells harbor [3,4]. This article aims to shed light on the update of the human microbiome and its relation to human diseases.

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The human microbiome

Microbiota is defined as the community of micro-organisms living in a particular environment. Food microbiota, soil microbiota, and marine microbiota is the microorganism living in food, soil, marine water respectively. The human microbiota is all microorganisms; bacteria, archaea, lower and higher eukaryotes, and viruses, that live on and in humans as gut microbiota, vaginal microbiota, skin microbiota and so. The microbiome is the microbiota in a particular environment and their collective genomes. The human microbiome consists of the human microbiota and the genes these cells harbor [5,6]. The interest in studying the human microbiome comes from the fact that these bacterial genes can be expressed giving products that affect human health [7,8].

The National Institute of Health (NIH) of the USA started the Human Microbiome Project (HMP) in the year 2007. This project aimed to identify the human microbiota. It also aimed to search the relation of this microbiome to human health and disease. [9]. The USA project was followed by projects of other countries as the Canadian National Institute of Health, through the CIHR Institute of Infection and Immunity and The Brazilian Microbiome Project (BMP) [10].

Many previous studies indicated that over 10,000 microbial species have been shown to occupy various parts of the human body [11]. The human microbiome is characterized by the huge number and diversity. The diversity can be relatively low as in skin or great as in the gut [11]. The human microbiome includes around 100 trillion bacterial cells which are 10 times human cells number with a total mass of about 0.2 kg [12]. The number of the human microbiota is highest in the colon, followed by the skin [13, 14]. The genes included in the human microbiome are about 100 times the genes of the human genome. They are also more diverse [11].

Many members of human microbiota especially gut microbiota are difficult or impossible to culture but modern technologies enabled scientists to identify many new microbial taxa. The omics approaches, including phylogenetic marker-based microbiome profiling, shotgun metagenomics, metatranscriptomics, metaproteomics, and metabolomics, has enabled efficient characterization of microbial communities [15, 16].

Metataxonomics is a term defined as the high-throughput process used to characterize the entire microbiota and create a metataxonomic tree, which shows the relationships between all sequences obtained. Metataxonomic can be done at the level of DNA by metagenomics, RNA by metatranscriptomics, metabolites or metabolon through metabolomics or at the level of extracted protein by metaproteomics [17, 18].

The collection of genomes and genes from the members of a microbiota is called metagenome [18]. This collection is obtained through shotgun sequencing of DNA extracted from a sample (metagenomics) followed by assembly or mapping to a reference database followed by annotation. Metatranscriptomics refers to the analysis of the suite of expressed RNAs (meta-RNAs) by high-throughput sequencing of the corresponding meta-cDNAs. This approach provides information on the regulation and expression profiles of complex microbiomes. Metabolomics is analytical approach used to determine the metabolite profile(s) in any given strain or single tissue. Metaproteomics refers to the large-scale characterization of the entire protein complement of environmental or clinical samples at a given point in time. This method identifies proteins from the microbiota and the host/environments. Computational analyses afford assignments of these proteins to their biological origins [16-19].

Importance of the human microbiome

The human microbiota have adapted from last times to its habitat in the human being doing many beneficial roles. Sometimes, it can harm the host in case of its disturbance or disturbance of its host immunity. The importance of the human microbiome comes from its high number, great diversity of the genes so it can produce high amount of metabolites that can affect its host to the degree some scientists has considered it especially the gut microbiome as an extraorgan [20]. The human microbiome plays beneficial functions in human health as it accomplishes many vital processes. It maintains intestinal integrity and supports its barrier function. It helps in breaking down some complex molecules in food. It provides essential nutrients as vitamin K and vitamin B [21]. It converts primary bile acids into secondary bile acids, thus allowing lipid absorption. The human microbiome is considered part of the innate immune system. It can prevent infection through the inhibition of pathogens through competitive inhibition or secretion of inhibitory substances as bacteriocins [22, 23]. It helps in regulating the immune system, as it can modulate lymphoid structure development and T

cell differentiation [24]. Germ-free mice showed reduced CD4 in intestinal lamina propria and defects in CD4 cells in the spleen. It also shows a reduced number and decreased cytotoxicity of intestinal CD8+T cells [25]. Naïve CD4 T cell differentiates to Th 17 in the presence of segmented filamentous bacteria while it differentiates to Treg in the presence of clostridium spp [26]. The gut microbiome can affect IgA secretion as microbiota antigens and microbial metabolites promote plasma cell differentiation in both mucosal and systemic sites. Lack of intestinal microbial stimulation results in fewer numbers of IgA+ plasma cells in the gut and a reduced abundance of IgA [27].

Many factors can change the human microbiome. The major factor is dietary changes. Other factors include physical activity, lifestyle, hygiene, pets, bacterial infections, and antibiotic or surgical treatment, exercise, stress, smoking, and pollution [28]. Infant delivered by C-section, and formula-fed infants have a bad effect on the microbiome [29,30]. Diet rich in fiber, fruit, vegetables, whole grains, and legumes, as well as healthy fats like olive oil gives you a good microbiome, on the other hand a lot of red and processed meat, fried foods, high-fat dairy products, potatoes, and sweetened drinks are bad for the gut microbiome [31]. Antibiotics can transiently or permanently alter the composition of healthy adult microbiotas, usually via depletion of one or several taxa [32].

Disturbance of the human microbiome can lead to somatic diseases as autoimmune diseases, obesity, metabolic syndrome, Diabetes mellitus type II (DM type II), and the development of cancer. Besides, somatic disorders, dysbiosis was associated with autism and psychiatric disorders. High neuroticism and low conscientiousness groups were correlated with a high abundance of *Gammaproteobacteria* and *Proteobacteria*, respectively [33].

Relation of the human microbiome to autoimmune diseases

Disturbance of the microbiome is an important cause of auto-immune diseases. It is claimed that immunity is not only genetic self but also microbiome self so the change in the individual microbiome can be a factor to loss self-tolerance with the development of auto immune diseases [34].

In a genetically predisposed individual, under some environmental factors as diet, drug therapy, the microbiome can be changed. Sustained change in the human microbiome can lead to immune dysregulation as a decrease in IgA, decrease in Treg. Th17 cells induced by segmented filamentous bacteria (SFB) are non-inflammatory, while Th17 cells induced by Citrobacter are a potent source of inflammatory cytokines that can lead to disease development [35].

Dysbiosis has been reported in many autoimmune diseases [34]. Rheumatoid arthritis patients show increases in *Aggregatibacter actinomycetemcomitans* and *Porphyromonas gingivalis* periodontitis [36]. In Sjogren's syndrome, Bacteriodetes increased, while Firmicutes/Bacteroidetes ratio and Actinobacteria decreased [37]. Patients of Behcet's syndrome show increased gut Bilophila spp., a sulfate-reducing bacteria, Parabacteroides spp. and Paraprevotella spp. while there is decreased level of *Clostridium* spp. and methanogens [38]. Inflammatory bowel diseases are characterized by the outgrowth of the phyla proteobacteria, in particular the *Enterobacteriaceae* family and *Fusobacteriaceae* [39]. In a Chinese study, the genera Rhodococcus, Eggerthella, Klebsiella, Prevotella, Eubacterium, Flavonifractor and Incertaesedis were significantly enriched, while genera Dialister and Pseudobutyrivibrio were significantly depleted in SLE patients [40]. Gut dysbiosis occurs in other auto-immune diseases as multiple sclerosis and type I diabetes mellitus [41].

Relation of the human microbiome to cancer

Dysbiosis may influence carcinogenesis via microbial toxins, altered metabolites, hormonal dysregulation, sustained inflammation, immune modulation, DNA damage, and mutagenesis [42]. The normal gastric microbiome includes *Proteobacteria*, *Firmicutes*, *Actinobacteria*, *Bacteroidetes*, and *Fusobacteria*. There is an inverse relationship between *H. pylori* abundance and microbial diversity in non-cancer gastric biopsies, but gastric cancer was associated with a lower diversity compared to other samples with similar *H. pylori* abundance [43]. Regarding other types of cancer, the gut microbiota shows a lower abundance of *Firmicutes* and *Proteobacteria*, along with relatively higher levels of *Bacteroidetes* and *Fusobacteria*, have been found in lung cancer patients compared to healthy individuals [44]. Overabundance of *Fusobacterium* sequences in colo-rectal cancer (CRC) were detected versus matched normal control tissue by quantitative PCR analysis from a total of 99 subjects [45].

Fusobacterium nucleatum (F. nucleatum) sequences were significantly enriched compared to samples obtained from control subjects, while both Bacteroidetes and Firmicutes were relatively depleted in those with *Fusobacterium*-rich malignancies [46,47]. In a Moroccan study, CRC group, Fusobacteria, Firmicutes and Proteobacteria were overrepresented, while Bacteroidetes were more prevalent in controls [48]. The association of *F. nucleatum* with CRC was attributed to its ability to stimulate the proliferation of tumor cells through the FadA (fluffy autolytic dominant A) adhesion gene promoting the gut inflammatory response [49]. *F. nucleatum* infection can increase the expression of pro-inflammatory genes such as Interleukin-6 (IL-6), tumor necrosis factor (TNF-α), and Mmp3. A higher consumption of red and processed meats, which are high in sulfur-containing amino acids and inorganic sulfur, has been shown to increase abundances of sulfidogenic bacteria such as *Bilophilawadsworthia* and *Pyramidobacter* spps which produce genotoxic hydrogen sulfide in the gut thatcan damage DNA in intestinal epithelial cells and promoting carcinogenesis [50,51].

Relation of the human microbiome to metabolism

Gut microbiome produce various metabolites as short chain fatty acid (SCAFs), 5-hydroxytryptamine (5-HT) and gammaaminobutyric acid (GABA). These chemical metabolites help to regulate a person's metabolism and brain functions because some of these metabolites act as neuro-transmitters as serotonin and GABA. [39,51]. In addition to microbiome metabolites, certain bacterial structures as lipopolysaccharides (LPS) can affect enero-endocrine cells through interaction with toll-like receptors (TLRs). Thus the gut microbiome can affect secretion of gut hormones as Glucagon-like peptide-1 (GLP-1), 5-HT, and peptide YY*(* PYY). The microbiome thus indirectly can affect the glucose metabolism, satiety, adiposity and insulin sensitivity [52, 53]. Altered intestinal microbiota composition has been demonstrated with obesity, anorexia nervosa, and forms of severe acute malnutrition such as kwashiorkor [54]. In Ukraine, a study done on 61 adult individuals revealed that fecal concentration of *Firmicutes* was increased while *Bacteroidetes* was decreased with increasing body mass index [55]. Alterations in the bacterial composition/diversity are generally associated with changes in the metabolic profile of the microbiota that also influence host health [56]. Fecal transplants from obese mice leads to increase in total body fat of germ free mice [57].

Adherence to a Mediterranean diet (more nutritionally balanced and lower in dietary fat) can influence the physiology of the gut bacteria positively resulting in lower insulin resistance [58]. Certain strains of bacteria such as *Ruminococcus gnavus* are considered "pro-inflammatory" in nature so it can lead to the chronic inflammatory state seen in metabolic disease and obesity [59]. In comparison to healthy individuals, diabetic patients have less *Akkermansia muciniphila* that has anti-inflammatory effects [60,61]. Abundance of Lactobacilli occur in DM type II individuals. *Lactobacillus* has been associated with elevated fasting blood glucose and (hemoglobin-A1c) HbA1c levels while *Clostridium* has displayed opposite effects [62].

The abundance of *Enterobacteriaceae* and *Streptococcus* spp. were higher in patients with atherosclerotic cardiovascular disease than in healthy controls. Microbial-associated metabolites called Trimethylamine-N-oxide, has been linked with the development of atherosclerosis and shown to affect the progression of cardio-vascular disease [63]. **Visconti et al r**eported that gut micobiome with predominance of several gram-negative bacteria, such as *Veillonella*, *Haemophilus* and *Klebsiella* increase the severity of coronary artery disease as these bacteria trigger the innate immune response via (LPS) production and elicit a subsequent inflammatory reaction that is mediated by local generation of cytokines [64].

Novel therapies involving the microbiome

The gut microbiome cane be positively influenced by novel therapies that can give positive impact on the individual health. Prebiotics are the indigestible dietary polysaccharides that promote the growth of gut microbes as fructooligosaccharides and galactooligosaccharides which have anti-inflammatory effect, and improve inflammatory bowel disease symptoms. Also, inulin and cellulose have anti-cancer effect [65]. Probiotics is defined as living microorganisms that must be ingested in a sufficient amount to have a positive effect on health that is not limited to the nutritional effects. *Saccharomyces or Lactobacillus* genera are examples of probiotics. They were used to treat diarrhea. They also improve insulin resistance [66]. Fecal microbiota transplantation (FMT) is the administration of a solution of fecal matter from a donor into the intestinal tract of a recipient in order

to directly change the recipient's gut microbial composition and confer a health benefit. FMT is used to treat recurrent antibiotic-associated diarrhea and *Clostridioides difficile* infection [67].

Conclusion

Our human microbiome co-evolved with mankind over millions of years, but the recent lifestyles comprising increasing hygienic conditions, access to antibiotics and other drugs, and introduction of high-fat diets, could have had an impact on human-microbiome symbiosis especially gut microbiome. The human microbiome can affect the human both in health and disease. Understanding the relation of the microbiome to disease can help scientists to understand the pathogenesis of these diseases and development of novel therapies as prebiotic, probiotic and fecal microbiota transplant which can treat the dysbiosis and restore the normal gut microbiota balance.

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