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Expanding the Research on Gut Microbiota in Health and Disease

What is the Human Microbiome?

The human microbiome consists of bacteria, archaea, viruses, and eukaryotic microbes that exist on and in our bodies. These microbes have tremendous potential to impact us in health and disease.[1-3] They contribute to metabolic functions, protect against pathogens, educate the immune system, and through these essential functions, affect most of our physiologic functions directly or indirectly.[1-3]

The study of the human microbiome has been furthered by technological advancements for performing culture-independent analyses. Nowadays, novel culture-independent molecular biochemical analyses (genomics, transcriptomics, proteomics and metabolomics) allow detection and classification of the diverse microorganisms in a given ecosystem (microbiota) including the gastrointestinal tract (GIT), the skin, the airways, the urogenital tract, and others and to study all genomes in these ecosystems (microbiome) as well as their gene products. These analyses revealed that each of these organs has its microbiota that plays a role in health and disease. In addition, they immensely contributed to the recent progress in the understanding of the etiology and pathogenesis of a wide range of human conditions. Therefore, it is expected that such new insights would translate into diagnostic, therapeutic and preventive measures in the context of personalized medicine.

The Gut Microbiome in Health and Disease

While the GIT was once regarded merely as a digestive organ only, new technologies have led the scientific community to wonder about the impact that the gut microbiota may have on human health and disease.[4] The gut microbiome is currently becoming recognized for its role in modulating metabolism, immune defense, and behavior. From *in utero* stage onward, variations to those that rapidly occur after birth; the human gut microbiome changes with age, environment, stress, diet, and health status as well as exposure to other agents such as medicines. The microbial community of the human gut plays a critical role in functions that sustain health and is a positive asset in host defense.[4] Our understanding of this human "superorganism" has advanced following characterization of fecal metagenomes which identified three core bacterial enterotypes, which can have impact and consequences on GIT disorders and diseases.[5]

The advancement in our understanding of the gut microbiome during the last decade is reflected in the exponential rise in the global production of literature covering a wide range of aspects of gut microbiota in health and disease. For instance, a search using PubMed for the terms "gut microbiome" or "gut microbiota" resulted in a total of 13,723 records. Majority of these (11,402) were published in the last 5 years, and there were only 341 articles older than 10 years [Figure 1]. Furthermore, Figure 2 shows a word cloud of the keywords in the titles of the top 200 "best match" articles retrieved from the PubMed search depicted in Figure 1. Their relative importance and level of interest inferred from their frequency are presented in Table 1. We will not indulge in further detail on specific technical considerations in this space; however, interested reader is referred to recent review articles on the subject.[4,5]

Gut microbiota primarily exists in a reciprocal state with the host contributing several vital functions such as carbohydrates fermentation, vitamin biosynthesis, and the regulation of the immune system. Indeed, gut microbiota represents a dynamic organ, which responds to changes in the host, such as age, as well as diet, antibiotics, and other environmental factors. While these microbes are capable to adapt to change, any disturbance in the host-microbe equilibrium has the potential to initiate a sequential series of events that lead to a disease.

The current knowledge and future perspectives on the composition and function of human gut microbiota are focused on altered microbiota and gastrointestinal disorders, nutritional influences on the gut microbiota, and the consequences for digestive health, as well as improved understanding of gut-microbiota-brain communication. Using the same method, a PubMed search for "gut-brain axis" revealed 851 records. In the current issue of this journal, there is a very comprehensive review by Eshaghpour *et al*. From the research group at

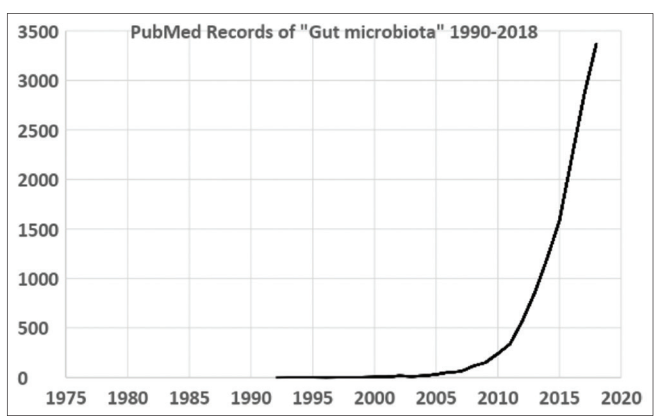

Figure 1: The exponential increase in the literature on gut microbiota in the last three decades reflected in the numbers of PubMed records retrieved by a search performed on October 26, 2018

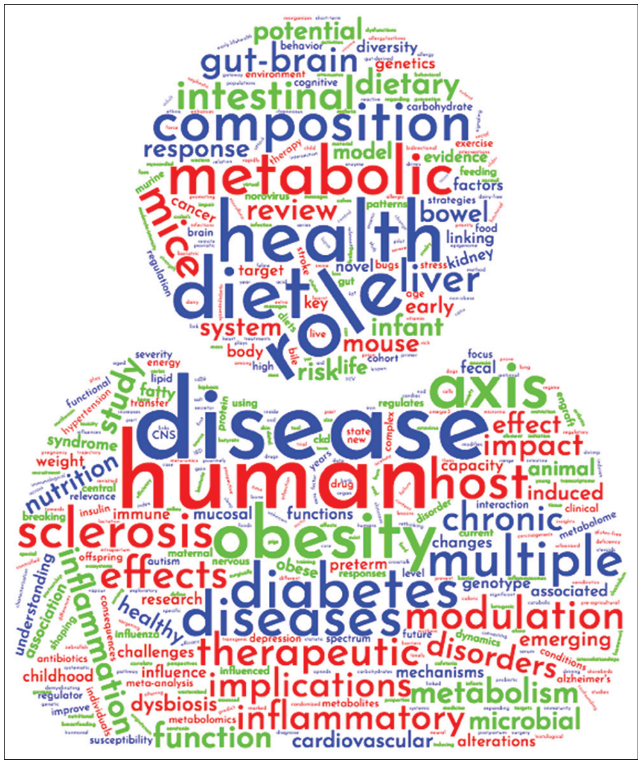

Figure 2: A word cloud of the keywords in the titles of the top 200 "best match" articles retrieved from the PubMed search. Gut, microbiome, and microbiota were not drawn being the search-defining terms

Dammam, Saudi Arabia, on the gut microbiome and gut-brain axis with a particular interest in Parkinson's disease as an example of neurodegenerative diseases.[6] The role of current therapies and the development of future treatments targeting the gut microbiome as a potential mode of treatment are highlighted.[6] However, these discussions are still far from the day-to-day clinical practice. We now realize that Parkinson's disease has both motor (movement) as well as nonmotor features such as dementia. There are also reports of constipation and inflammatory bowel disease-like symptoms.[7] There has been also some work done on the association of microbiota and Alzheimer's disease. Given the decreased integrity of both the gut endothelial barrier and the blood–brain-barrier, there is a possibility that the gut microbiota may have a role to play in sporadic Alzheimer's disease in the elderly.[8]

Furthermore, various systems of the body may be affected by disturbance in the variety of microbiota (dysbiosis) in addition to the central nervous system, such as the cardiovascular systems. Examples include atherosclerosis, myocardial infarction, heart failure, and stroke [Table 1 and Figure 2]. These systemic effects may occur through metabolic or nonmetabolic pathways. The former is related to metabolites released by gut microbiota and absorbed (e. g., trimethylamine/trimethylamine, which is produced from dietary choline[9] and L-carnitine).[10] Subsequent metabolism in the liver and release harmful substances to the systemic circulation such as trimethylamine N-oxide which was found to be related to

Table 1: The themes of the top most relevant 200 articles on gut microbiota in health and disease retrieved in the PubMed search in decreasing frequency

Theme of the article[a]	*n*[b]
Diet, nutrition, body composition	35
Basic research, methodology, animal models, disease mechanisms, metabolomics	25
Energy metabolism, obesity and bariatric surgery	19
Infection, immunity, and allergy	17
Metabolism, metabolic diseases, lipids, hypoglycemia	16
Brain and central nervous system	16
Multiple sclerosis, neurodegenerative disease, Alzheimer, cognitive function	16
Early life, child and infant health	15
Cardiometabolic, atherosclerosis and vascular disease (including hypertension)	14
Diabetes	12
Liver disease, fatty liver, gallbladder	11
Inheritance, genetics, metagenome	11
Inflammatory bowel disease	8
General topic, review, introduction	7
Inflammation, arthritis, skin	7
Kidney disease	7
Therapeutics, fecal microbiota transplantation, complementary medicine	6
Ecological framework, environment	6
Age, exercise, bone health	5
Drugs and drug metabolism	5
Dysbiosis	5
Colorectal adenoma and carcinoma	5
Psychology, autism, behavior, neurodevelopment, sleep, social behavior	4
Psychiatry: Depression, anxiety, stress, obsessive-compulsive disorder	4
Maternal health and pregnancy	4
Noncommunicable disease, chronic diseases	3
Human Immunodeficiency virus (HIV)	2

[a]No distinction was made between human and animal studies, [b]Counts are not mutually exclusive

cardiovascular disease through platelet activation, cholesterol efflux, and uremic toxicity, and other possible ways.[11,12] In addition, nonmetabolic pathway involves the translocation of bacteria from the gut can occur, and it was suggested that might occur in heart failure causing various problems such as inflammation.[13]

The intensive and active research illustrated in Figure 1, keeps us furnished with new news every day on novel and possible relationships between microbiota and various disease conditions. Moreover, the effect of environmental factors is being studied, and the effect of pollutants in the air which is inhaled and subsequently cleared by cilia and swallowed were found to have an impact on the microbiota.[14] The need to device interventional strategies to prevent or treat disease through the microbiota "organ" using dietary protocols and medicines represents a novel and exciting approach. The exponential rise in research productivity is ongoing and is expanding, and it would be most interesting when these start to get translated into address clinically meaningful questions.

Author's contributions

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Conflicts of interest

There are no conflicts of interest.

Compliance with ethical principles

No human or animal studies are reported by the authors.

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