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HUMAN GUT MICROBIOME: RELATION WITH VARIOUS DISORDERS AND ITS ASSOCIATED THERAPY USING PROBIOTICS

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ABSTRACT

The developments in DNA sequencing technology and computational biology have revolutionized the world of microbiome, which in turn resulted in identifying the contributions of the microbiome to human health. Dysbiosis of the intestinal microbiota making up the human microbiome can have a marked influence on energy and immune homeostasis, which results in significant metabolic and immunologic effects on the host, ultimately leading to many local and systemic diseases including inflammatory bowel disease, asthma, obesity, metabolic syndrome, cardiovascular disease, immune-mediated conditions, and neurodevelopmental conditions such as autism spectrum disorder. In this systematic review, we provide an overview of the evidence on the association between human gut microbiota and various disorders. Besides, we analyse the effects of microbiome-based therapies on the above disorders using probiotics.

KEYWORDS: Gut dysbiosis, microbiome, cardiovascular, obesity, HIV, chronic inflammation, psychiatric disorders, cancer, Probiotics.

INTRODUCTION

Gut microbiota is considered as an array of microorganisms that inhabit the gastrointestinal tract. The composition gut microbiota depends on the host, but it can also be modified by exogenous and endogenous events.[1] Depending upon the host these bacteria are symbiotic and have an important role in physiological processes. Gut microbiota is mainly members of four phyla (*Firmicutes*, *Bacteroidetes*, *Actinobacteria* and *Proteobacteria*).[2] Recently many experiments were conducted to point out the significant effects of antipsychotics on the composition of gut microbiome and also the effect of microbiome on the pharmacokinetics of the antipsychotic drugs.[3] Supplementation with probiotics and other alternative dietary treatments are being taken in obesity.[4] Change in the microbial composition or dysbiosis has a corelation with the genesis and evaluation of cancer like complex diseases. Together, microbiome related research can be extended to the personalised treatment of cancer from the view of precision medicine by integrating the knowledge of chemistry, bio informatics, HT data and system biology.[5]

Challenges in clinical microbiome studies

It's not an easy task to integrate human microbiome into clinical studies and designs. The human microbiota remains stable for years. In addition to the long-term stability and plasticity within the gut environment, the Inter and intra variability among individuals is an important factor to consider. Intra variability may be due to infant transitions, i.e. birth gestational age, type of delivery, and the way of milk feeding. Intervariability of gut microbiota can be due to sex, enterotypes, BMI, and external features such as life style.

Variables that affect the composition of gut bacteria

Hosts genetic background: Gupta et.al reported that intestines of hunter- gather population have a wide distribution of *prevotella*, *Proteobacteria*, *Spirochaetes*, *Clostridiales*, and *Ruminobacter* while in the urban population, there found more amount of *Bacteroides*, *Bifidobacterium*, and *Firmicutes.*[6]

Geography: The effect of geography on microbiota is through diet, i.e., depends on what a person eats.[6]

Sex: both drugs and diet affect the microbiota in men and women differently. Women with high estrogenic level and men with high testosterone level, show greater gut microbial diversity.

Age: Biodiversity of gut microbiota decreases as the age increases.

Stress: stress will lower the gut microbiome diversity by increasing the growth of protease bacteria through gastric acid release and GIT motility, and also by modulating inflammation through hypothalamic pituitary adrenal axis.[3]

Psychiatric Disorders and The Microbiome

The faecal microbiota of 28 first-episode psychosis (FEP) patients was examined in a recent study,14 of which were clinically diagnosed with schizophrenia. The results it has shown that bacteria specifically Lactobacilli, *Lachnospiraceae*, *Ruminococcaceae*, and *Bacteroides* spp. were correlated to negative symptoms and poorer function. Moreover, *Lactobacillaceae*, and Micrococcineae were increased, and *Veillonellaceae* were decreased in FEP patients compared to controls.[7]

Positive modulation of the gut microbiome with the introduction of living microorganisms was found to be successful in eliminating the negative effects of some disorders.[8]

For example, *L. Plantarum* 299v probiotic was found to decrease exam stress levels in healthy controls following a 2-week administration. Anxiety and depressive readouts were decreased with a markable decrease in cortisol levels following 30 days of probiotic (*L. Helveticas* and *B. longum*) treatment in healthy adults.[9]

Bipolar disorders are also linked with alterations in the microbiome. Recent probiotic studies suggest that probiotic therapy could reduce the rate of re-hospitalization of patients over a 24-week adjunctive probiotic treatment with *L.rhamnosus* strain GG and *B. animals* subsp. lactis strain Bb12 who were recently discharged following hospitalization for mania.[10]

Recent studies suggest that medication used in the treatment of psychiatric disorders can also affect the composition of the gut microbiota and their involvement in drug pharmacokinetics in general. Benzodiazepines and antidepressants were listed as co-variates influencing microbiota in the Belgian Flemish Gut Flora Project.[11]

Microbiota Manipulation as a Therapy for Psychiatric Disorders

From the recent studies, it was found that microbiota manipulation represents a promising tool or adjunct therapy in the treatment of many disorders and/or their associated symptoms. The advantage of microbiota manipulation as a treatment strategy is that the microbiota can be positively altered quite readily by several factors including diet, exercise, and stress reduction. Limited clinical studies in this research field have been performed in healthy adults, at 1 dose, and with only 1 or 2 probiotic treatment groups. However, the majority of these studies have reported positive effects. Clinicians, also cannot neglect the treatment of their patients with the appropriate psychiatric medicine while considering the potentially beneficial effects of microbiota manipulations.[12]

Faecal transplantation

It is an emerging therapy for many disorders – transferring healthy microbiota into a dysbiotic gut. Stool from a healthy donor is used to seed healthy bacteria in an ill patient, for the restoration of missing bacteria, nonbacterial elements, and metabolites. In general, stool transplanted from donors with high microbial diversity results in a beneficial response. [13]. However; there are potential risks involved in this new therapy. One recent study warned that faecal transplants, while they might be able to reduce mental illnesses (though this has not been shown for schizophrenia), could also transmit illness.[14]

Effect of the microbiome in antipsychotic drugs

Microbiome-encoded enzymes also alter the absorption, distribution, metabolism, and elimination of drugs like the human enzymes so that clinical response and adverse effects are either enhanced or declined. The primary mechanisms of action of bacterial enzymes are hydrolytic and reductive. One example is that in the Benz isoxazole ring system of the risperidone molecule, the chemical reduction of isoxazole was carried out mainly by intestinal flora in the colon.[15]

Bacterial enzymes also have an indirect effect on pharmacokinetics by the modulation of their host's metabolic enzymes. For example, the expression and activity of phase I and phase II liver enzymes, such as the cytochrome P450 s (CYPs) superfamily and the glutathione S-transferases (GST), are altered when microbial enzymes change the composition of bile.[15]

Pharmacodynamic effects are also exerted by microbiota. Several neurotransmitters, namely serotonin, GABA, noradrenaline, and dopamine are produced by the gut microbes. These chemicals can travel to the brain, and could directly impact the action of drugs on brain neurotransmitter receptors. This will either reduce or boost both drug activity and drug side effects.

Cardio Vascular Disease and The Microbiome

Microbes have a significant effect on cardiovascular health like the local effect of the gut microbiota on energy metabolism and obesity and the distal association of the periodontal disease with coronary heart disease. The studies stated the beneficial effects of certain probiotic bacterial strains to reduce cholesterol and hypertension, recent research suggests that their use could be more widely applied.[16]

The teeth, tongue, cheek, attached gingiva within the oral cavity are colonized by distinct and complex microbial communities. About 500 oral bacterial species have been identified, with the healthy "core microbiome" consisting mainly of *Firmicutes*, *Proteobacteria*, *Actinobacteria*, *Bacteroidetes*, and *Fusobacteria*. All of these helps to produce nutrients, maintain pH, modulate saliva

production, and generate inhibitory substances, etc. to prevent colonization by pathogenic species.

With the classic example of *Streptococcus pyogenes*, the members of oral microbiota have a crucial role in cardiovascular health. Periodontal disease and CVD are interconnected. The increase in gingival bleeding during PD provides access for oral bacteria to the bloodstream, where they can circulate and interact with atheromatous plaque deposits. And these atherosclerotic lesions are detected with oral bacterial DNA. These bacteria may invade and activate endothelial cells, increasing Toll-like receptor (TLR) interactions, or inducing the expression of metalloproteinases, all of which contribute to the development of CVD. *Porphyromonas gingivalis*, a periodontal pathogen, generated by the host antibodies indicates the cross-reactivity with human heat shock proteins (HSPs), including HSP60 which are commonly expressed in atherosclerotic lesions by endothelial cells.[17]

Epidemiological studies demonstrated that vegetarians and have lower blood cholesterol and lower risk for CVD compared to omnivores. Excluding red meat from the diet is beneficial for cardiovascular health. Dietary carnitine and phosphatidylcholine from red meat, are converted to trimethylamine (TMA) by colonic microbes. It is then converted to the proatherogenic metabolite trimethylamine-*N*-oxide (TMAO), which accelerates atherosclerosis in mice. Individuals receiving oral antibiotics for a week before consuming red meat experienced a complete reduction of endogenous TMAO production. From the same study, it is seen that vegetarians had significantly lower fasting baseline TMAO levels, compared to omnivores. Vegetarians had a predominantly abundance of *Bacteroides* species and a lower abundance of *Prevotella* species in the gut microbiome than omnivores, and a decreased risk for coronary heart disease.[18]

Modulation of the human microbiome

Antibiotics are the modulators used. Modern medicine has encouraged the prescription of antibiotics to eliminate infectious microbial pathogens. Gut infections such as *Clostridium difficile*, *Escherichia coli*, *Salmonella* spp., and *Helicobacter pylori* can be controlled with the use of antibiotics. However, the use of broad-spectrum antibiotics should be avoided as it is indiscriminative of the pathogenic and non-pathogenic microbes.[19]

Application of probiotics in CVD

Probiotics are the live microorganisms which are administered in adequate amounts to provide health benefit on the host. Probiotics can interact with the existing microbial community through competition with pathogens. The most important application of probiotic therapy for CVD is the reduction of serum cholesterol. Ingestion of probiotics can sequester cholesterol from the gut by incorporation into the cellular membrane. They also convert cholesterol to coprostanol. The probiotic strain(s) should be selected carefully such that it can lower LDL cholesterol and not adversely affect cardiomyocyte function or increase fat deposition. A study showed that Mice that were Administered with *B. breve* NCIMB 702258 showed an increase in visceral fat mass and weight gain whereas the administration of *B. breve* DPC 6330 did not show any change.

Hypertension, which is closely bound to hypercholesterolemia, is a major risk factor for CVD. Probiotic therapy could potentially improve hypertension and outcomes for CVD patients as they improve lipid levels in the blood. Analysis of 14 randomized placebo-controlled clinical trials with 702 participants showed that probiotic fermented milk significantly reduced both systolic and diastolic blood pressure in pre-hypertensive and hypertensive patients. Reduction of cholesterol and hypertension reduced the risk of developing coronary heart disease, atherosclerosis, heart attack, and stroke by nearly half.[19,16]

Cancer and The Microbiome

The advances in metagenomics and bioinformatics have provided new insights on the microbial ecology in different tumors, elucidating the roles of microorganisms in cancer formation, development, and response to treatments. Furthermore, studies have emphasized the importance of host-microbial and inter-microbial interactions in the cancer microbiota.[20]

Infectious agents such as *Helicobacter pylori*, hepatitis B and C viruses, and human papillomaviruses have been recognized as carcinogenic agents and found that ∼20% of all cancers are caused by them.[21]

Metagenomic sequencing was a new approach to investigate the microbiota as an important pathogenic mechanism in many diseases. This gives a new insight into the microbial pathogenesis in diseases, which may arise from compositional changes and ecological dysbiosis, apart from the classical germ theory fixating on specific foreign pathogens. There is a is multifactorial and bidirectional relationship between cancer and microbiota.[22]

Diagnostic and prognostic potentials of fecal microbiota in cancer

In cancer biology, biomarkers are used as diagnostic markers to identify diseases, as prognostic markers to define the outcomes, or as predictive markers to predict treatment response. A gene marker from *F. nucleatum* could provide a complementary role to the fecal immunochemical test (FIT), with superior accuracy and sensitivity in detecting colorectal cancer and advanced adenoma when combined to FIT.[23]

These studies provided insight into the mechanisms of several systemic chemotherapies and immunotherapies and brought much hope in the potential of manipulating the microbiota to improve treatment efficacy and reduce

side effects. Gut microbiota is necessary for the optimal efficacy of some chemotherapeutic agents. In a recent study, investigators have studied the effects of cyclophosphamide, alkylating chemotherapy which promotes T-cell immunity and induces cancer cell death, on the microbiota and physiology in the intestine. The results showed that cyclophosphamide treatment led to shortening of small intestine villi and disruption of the epithelial barrier, which resulted in commensal bacteria translocating to the mesenteric lymph nodes and spleen. There, the bacteria stimulated the TH1 and TH17 immune cells to mediate the anti-cancer efficacy.[24]

Studies have been conducted to establish a relationship between gut microbiota composition and immunotherapeutic responses. In two studies that looked at patients with metastatic melanoma, strong microbial predictors of anti-PD-1 therapies were identified. Another study was carried out in which the authors surveyed the gut microbiota of patients with metastatic melanoma undergoing anti-PD-1 therapy. Patients responding to this therapy had a high abundance of *Faelibacterium* genus, whereas non-responding patients displayed a high relative abundance of other Bacteroidales orders in their feces.[25]

Anti-tumor effects of ipilimumab, a cytotoxic T lymphocyte antigen 4 (CTLA4) monoclonal antibody, depends on gut microbiota, especially two specific *Bacteroides* species of *B. thetaiotaomicron* and *B. fragilis*. Tumors in mice that are treated with the antibiotic did not respond to CTLA4 blockade, but the defect was eliminated by re-exposing the animals to *B. fragilis* or its antigens.[26]

Hiv and The Microbiome

HIV infection leads to intestinal microbial dysbiosis, and increase the abundance of pathogenic microbes. Intestinal barrier injury will cause the variation of gut microbiota and its metabolites (e.g., SAA, PSA, and SCFAs), and results in innate and adaptive immune activation. Dysbiotic intestinal microbiota can disturb the development of bone marrow cells by regulating local metabolites and tissue-specific mediators, causing a decrease in myeloid cells, CD34+ hematopoietic progenitor cells (HPC), and granulocytes. Also upset the differentiation of B cells into plasma cells in the spleen, which results in the decreased IgA and IgG.[27]

The regular' pathogens, such as *Escherichia coli*, *Salmonella*, and *Shigella*, and opportunistic 'pathobionts', such as *Cryptosporidium*, *Cytoisosporbelli*, *Microsporidium*, *Cytomegalovirus*, and *Mycobacterium avium-intracellulare* drive the AIDS-associated GIT symptoms.[28] Interruptions in intestinal immunity can result in gut dysbiosis, which may, in turn, produce chronic inflammation in the mucosa and periphery which are commonly observed in HIV-positive individuals.[29]

Cotrimoxazole administration could reduce intestinal inflammation through antibiotic effects on the microbiome or directly acting on mucosal leukocytes and gut epithelial cells. Cotrimoxazole is a combination drug of two folate pathway inhibitors, trimethoprim, and sulfamethoxazole. Cotrimoxazole treatment of rats affects absorption across the gut epithelium.[30] Studies were conducted using cotrimoxazole in HIV-positive children in sub-Saharan Africa to test whether cotrimoxazole reduces systemic inflammation. The results have shown that Systemic inflammation is lower among HIV-positive children randomized to continue oral cotrimoxazole prophylaxis daily. Disruption of the gut microbiome is the major reason which contributes to local and systemic inflammation in HIV. Studies have shown that cotrimoxazole have reduced the abundance of gut residing streptococci species.[31]

Probiotic *Saccharomyces boulardii* have shown beneficial effects in the modification of gut microbiome composition. Recent studies shown that Following probiotic treatment, there was a significant decrease in some Clostridiales, such as *Clostridiaceae* and *Catenibacterium* species.[32]

CONCLUSION

From the above topics covered we could conclude that the gut microbiome has an important role in defining the pathogenesis of many diseases. Gut microbiota has been proposed as a novel therapeutic target for reducing chronic inflammation.

The National Institute of Health (NIH) launched a research project in 2007 named HUMAN MICROBIOME PROJECT. The main objective of this initiative was to define the microbial species that affect humans by using the available large databases. Recent studies confirm that the manipulation of nonpathogenic bacterial strains in the host can stimulate the recovery of an immune response to pathogenic bacteria that causing disease. Different approaches include the use of nutraceuticals (prebiotics and probiotics) in treating various diseases, are trending now. The designing and production of pharmaceuticals targeting the body's microbiome is an emerging field to explore.

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