Chapter 23

Gut microbiome and COVID-19

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Introduction

Human microbiota are diverse clusters of microorganisms distributed over all human body systems. The microorganisms include protozoa, archaea, eukaryotes, viruses, and abundantly bacteria that occupy a variety of systems like the oral cavity, genital organs, respiratory tract, skin, and predominantly gastrointestinal system [1]. The microbiome is in dynamic equilibrium with the host and varies among different body sites of a host, among different hosts, different geographic locales, cultures, and ethnicities, and also over time [2,3].

The densest cluster of microbiota resides in the colon. The preponderance of the gut microbiota is nonpathogenic and symbiotic with intestinal epithelial cells. The gut microbiome comprises of collective genomes of microbiota encoding gene products modulating a diverse spectrum of biological and metabolic functions, many of which modulate host immune status and general well-being [4,5].

The microbes residing in the gut play fundamental roles in metabolism, endocrine, neuronal, immune, and many other aspects of body function. They can also function as a sensitive reflection of the human daily diet. It can also act as an energy generator by producing micronutrients, such as vitamin K and folate. In addition, Gut commensal bacteria ferment the unabsorbed carbohydrates into short-chain fatty acids (SCFAs), which are consequently absorbed by colonic mucosal cells and utilized as an additional source of energy [6,7]. Human fetus grows in near-sterile environment of the womb and gets the first exposure to bacteria during passage through the birth canal. Mammalian breast milk contains the exact nutrients a baby needs, the right bacteria, and it feeds the baby's microbiome [8]. The development and maturation of the gut microbiome is initiated during infancy, and gradually matures in the following 3 years, and can undergo changes over a life-span [9].

Agents that might disturb the equilibrium of microbiomes leading to dysbiosis (microbial imbalance) are various and might include: poor diet quality, drugs, the host environment, and diseases (infectious diseases, intestinal immune-mediated diseases, multisystemic autoimmune disorders, metabolic diseases, colorectal cancer, and neuropsychiatric disorders) [10–12].

Gut microbiome

The GIT, which has an interface of 250–400 m^2, consists of an integrated, versatile ecosystem with a robust community of microorganisms known as the "gut microbiome" [13–16]. Noble laurate, molecular biologist, Joshua Lederberg outlined "gut microbiome" as the integrality of microorganisms and their collective microbial genome present in the gastro-intestinal tract (GIT) [17,18]. The gut microbiota, a diverse assemblage of microorganisms in the gastrointestinal tract (GIT), has recently emerged as one of the most dynamic research areas, as it has multifactorial effects on different body systems, often playing a key role in determining the balance between health and disease states [15,19]. The gut microbiome has co-evolved with its host over millennia to establish and maintain a close, symbiotic association that supports its host in many different ways [16,19,20].

Factors modulating gut microbiome

The gut microbiota has extremely vital functions in the body, including supporting resistance to pathogens, affecting the immune system, playing a role in digestion and metabolism, modifying insulin resistance and its secretion, and affecting the behavioral and neurological functions of the host [4,21,22] (Fig. 1). Gut microbiota

exhibits alpha-diversity and beta-diversity; age, host genetics, allergies, diet, obesity, antibiotic abuse, inflammatory bowel diseases (IBD), and psychological stress are considered the most frequent factors which cause disarray in the gut microbiota community [3,23,24]. However, the gut microbiota structure and functions can be restored by modulatory factors such as probiotics, prebiotics, synbiotics, immunobiotics, parabiotics, nutribiotics, and postbiotics (Table 1) [21,22].

Viral, Parasitic, Bacterial, and Fungal Infections. https://doi.org/10.1016/B978-0-323-85730-7.00033-3

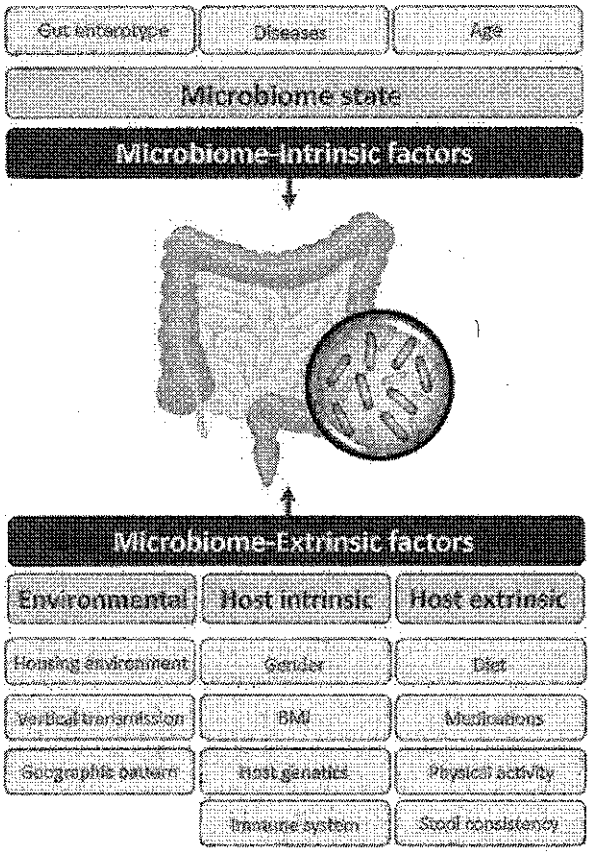

FIG. 1 Factors influencing gut microbiome composition.

Probiotics

Probiotics are defined as live microorganisms that when being administered in appropriate doses, will afford a benefit to the health of the host [26,27]. Usually, probiotic bacteria are components of the intestinal microbiota and, recently, they are being progressively integrated into food to enhance gut health by maintaining the gastrointestinal microbial equilibrium [15,28]. Probiotics can be found naturally in the human microbiota in systems like GIT, genitourinary, and skin. Fermented foods such as yogurt, cheese, and some vegetables are also considered an eminent source of probiotics, especially lactic acid bacteria (LAB). LABs, particularly those in the genus Lactobacilli, are the most common species used as probiotics. *Streptococci, Pediococcus, Enterococcus, Bifidobacteria*, and some yeasts are also included, like *Saccharomyces boulardii*. However, not all bacteria are allowed to be incorporated into probiotics, as they need to be strain specific [29]. Nominated microorganisms should be able to endure the harsh, highly acidic gastric juice and bile salt, adhere to gut epithelial cells' mucus, as well as survival digestive enzymes, multiply, and function efficiently in the GI tract for them to eventually be chosen as a strain to be included in the probiotic supplementation. Use of germ-free animals and gnotobiotic animals has been crucial in evaluating the efficacy of different supplements singly and in combinations (prebiotics, probiotics, cobiotics, synbiotics, immunobiotics, nutribiotics, and parabiotics) in preclinical studies [20,26,30].

TABLE 1 Terminology.

Alpha diversity: the Alpha diversity of microbiomes refers to a single sample and denotes how many different types of microorganisms are present in that sample.
BCAA: Branched chain amino acids; Valine, Isoleucine and Leucine (Fig. 3).
Beta Diversity: It measures similarity or dissimilarity of types of microorganisms in two different microbiome samples.
Biofilm: Community of microorganisms attached to a biotic or abiotic surface and enclosed in a bacterially produced polymeric material primarily composed of protein, carbohydrates, and nucleic acids. Bacteria in biofilm usually exhibit increased resistance to antibiotics and disinfectants and have reduced clearance by the immune system.
Biomarker: A biological molecule found in blood, other body fluids, tissues, or any biological sample that signifies a particular condition or disease.
COVID-19: Corona virus disease-19, the pandemic disease caused by SARS-CoV-2, which started in 2019.
Cytokine storm: Loss of coordinated functioning of the cytokines, which play a key role in the response of the immune system to infection. The proinflammatory cytokines occasionally start "storming" out of control without sufficient feedback from the anti-inflammatory cytokines, leading to occasional severe and life threatening multiple organ failure, even death.
Dysbiosis: Transition of a healthy microbiome (eubiotic microbiome) to an unhealthy microbiome (dysbiotic microbiome); imbalance in the intestinal microbiota usually characterized by reduced microbial alpha diversity; representing a disease state or a health condition.
Enterotype: Classification of human gut microbiome according to the type of microorganisms present. The microbiome of enterotype-1, enterotype-2, and enterotype-3 represents dysbiotic, eubiotic, and mixed type microbiomes, respectively [25].
Eubiosis: Transition of a dysbiotic (unhealthy) microbiome to a healthy (eubiotic) microbiome, the opposite of dysbiosis.
Fecal Microbial Transplantation (FMT): Transfer of fecal material from a healthy person with a eubiotic gut microbiome to the gastrointestinal tract of a person with a dysbiotic microbiome with the aim of reducing dysbiosis in the recipient.
Firmicutes/Bacteroidetes ratio: Firmicutes and Bacteroidetes are two major phyla of bacteria of the human gut microbiome. They represent more than 90% of the total microbiome. An increase in the Firmicutes/Bacteroidetes ratio indicates the transition of the gut microbiome towards dysbiosis.
Germ Free Animals: Animals that have no microbiome, i.e., no microorganisms living in or on them. Such animals are put in sterile conditions immediately after birth and are provided with sterile food and air. Such animals are useful in microbiome studies.

TABLE 1 Terminology—cont'd

Gnotobiotic animals: Animals in which only known microorganisms are present. Such animals are developed by introducing known, specific organisms to germ free animals. Very useful in determining the role of different members of the microbiome singly and in combination.
Gut-brain axis: Bidirectional communication between the central and enteric nervous system, linking emotional and cognitive centers of the brain with peripheral intestinal functions and the role of gut microbiota in influencing these interactions.
Homeostasis: The self-regulating process by which biological systems maintain the stability and constancy needed to function properly.
Immunobiotics: Immunobiotics are Microbial strains with the capability of beneficially regulating the mucosal immune system of the host.
Inflammasome: Cytosolic multiprotein complexes of the innate immune system, that induce activation of the inflammatory responses, resulting in a pro-inflammatory form of programmed cell death, termed pyroptosis.
Long COVID: A sequel of COVID-19 characterized by persistence of symptoms for more than 12 weeks since onset of infection.
Metabolic Syndrome: Combination of three health conditions: obesity, diabetes, and hypertension (high blood pressure).
Metabolome: Total metabolites found in a tissue or a sample.
Metagenomics: Genomic analyses of DNA extracted directly from a clinical or environmental sample that help assess alpha diversity and beta diversity among samples (through 16S rRNA metagenomics), or fuller complexity (through whole genome shotgun metagenomics).
Microbiome: The total genetic material of the microorganisms present in a particular environment.
Microbiota: Total microorganisms such as bacteria, fungi, archaea, protozoa, and viruses that are harbored by normal, healthy individuals.
Nutribiotics: Probiotics with nutritive claims
Operational Taxonomic Unit (OTU): It is an operational definition which is used to classify groups of closely related bacteria on the basis of their genomic similarity.
Parabiotics: Dead or inactivated living cells of probiotics.
Pathobiont: Normally harmless components of the microbiota which have pathogenic potential in some contexts.
Pathogen-associated molecular patterns (PAMPs): Pathogen-specific conserved molecules on *pathogens* which stimulate the innate immune response.
Prebiotics: Food ingredients that are non-digestible by humans but promote the growth of beneficial microorganisms (probiotics) in the intestine.
Probiotics: Living microorganisms (bacteria and yeast) that can be consumed by humans for health benefits.
Postbiotics: Metabolic products produced by probiotic bacteria as they act on prebiotic materials, which provide physiological benefit to the host.
RAS: Renin-angiotensin system is a hormone system which is essential for the regulation of blood pressure and fluid balance.
SCFA: Short-chain fatty acids; acetic acid, propionic acid, and butyric acid (Fig. 2).
SARS-CoV-2: Severe Acute Respiratory Syndrome Corona Virus-2.
Synbiotics: Combinations of prebiotics and probiotics together are termed as "synbiotics."
TMPRSS2: Transmembrane serine protease of mammalian cells; it functions in spike (S) protein (of SARS-CoV-2) cleavage, thus facilitating virus and host-cell membrane fusion, leading to entrance of the virus into the host cells.
Toll-like receptors (TLRs): TLRs are a class of proteins usually expressed on antigen-presenting cells (such as macrophages and dendritic cells) that play a key role in the innate immune system by recognizing structurally conserved molecules derived from microbes.
Variants: The variant of a virus is described as one that has gained enough mutations to have acquired new properties such as enhanced transmissibility, virulence, or host range.

Probiotics compete with pathogen species for adhesion sites. Some probiotics, when they grow in biofilms, can produce antimicrobial compounds like reuterin, produced by *Lactobacillus reuteri*, which directly destroys pathogenic microbes [31–33], and induces immune responses in the host [34]. *Bifidobacterium* enhances the function of the mucous intestinal barrier, increases serum IgA, and reduces inflammation in the intestines. In patients with type 2 diabetes, probiotic indulgence is reported to reduce fasting blood glucose, HbA1 level, and insulin concentration [35].

Prebiotics

Prebiotics are defined as selective fermentation components that cause specific changes in the activity or structure of the gut microbiota and so benefit the host [27,36].

A subgroup of dietary fiber sources is fermentable, which means that they work as growth substrates for microbes in the distal bowel for the treatment or prevention of colorectal cancer and ulcerative colitis [29]. Nondigestible carbohydrates include many types, such as oligosaccharides or short polysaccharides like inulin, oligofructose, galactofructose, galacto-oligosaccharides, and xylo-oligosaccharides [27,36]. The focal aim of prebiotics is the effect of increased production of SCFAs that regulate a range of local and systemic functions. Dietary fiber consumption is also important to maintain intact mucosal barrier function in the gut and glucose and lipid metabolism. Studies showed that administration of inulin (a prebiotic fiber) can prevent the harmful effects of high-fat diet on penetrability of the mucus layer and metabolic functions such as high pathogen susceptibility and inflammation sequalae [37]).