

Human Microbiome in Health and Disease

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Abstract

The microbiome consists of a diverse groups of microorganisms, which including bacteria, archaea, protozoa, fungi, algae, and viruses (In spite of the fact that viruses are usually included, but their classification still debatable due to their acellular nature and absence the autonomous life processes). When integrated into a host, (typically an eukaryote, the system is called as a holobiont the disturbances in the microbial homeostasis that termed as dysbiosis are engaged with the emergence and progression of various diseases. Accordingly, the investigation of microbiomes has gained considerable attention in many fields like molecular biology, human health, clinical medicine, along with environmental science, due to their intense impact on host's physiology and disease predisposition As results of their metabolic and molecular activities, they deem as an integral part of the host body, and contributed to the developmental, immunological, and metabolic alterations over the lifespan. It is worth noting, the human microbiome remaining in continual flux, affected by a wide range of specific factors of host like as diets, age, genetic, underlying disease, as well as the environmental exposures. However, shifting in the composition of the human (dysbiosis) microbiota may cause a life alarming disease. This overview seeks to illuminate the intricacies of the microbiome Because of its importance to human health.

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1. The Definition and Biological Significance of Microbiome

The microbiome points to the dynamic, polymicrobial assembly that usually called microbiota, beside its collective biochemical activity and genetic structures, existing within a defined spatiotemporal niche. This community consists of a diverse groups of microorganisms, which including bacteria, archaea, protozoa, fungi, algae, and viruses (In spite of the fact that viruses are usually included, but their classification still debatable due to their acellular nature and absence the autonomous life processes). When integrated into a host, (typically an eukaryote, the system is called as a holobiont, and its combined genetic reservoir termed as hologenome. The reciprocity among these microbial components and host ranges from long-stand evolutionary association to transitory or emergent association, some of them may trigger rapid physiological alterations or pathological conditions. Particularly, the disturbances in the microbial homeostasis that termed as dysbiosis are engaged with the emergence and progression of

various diseases. Accordingly, the investigation of microbiomes has gained considerable attention in many fields like molecular biology, human health, clinical medicine, along with environmental science, due to their intense impact on host's physiology and disease predisposition [1].

2. The Human's Microbiome: Complexity and Clinical Significance

The human microbiome includes the complex communities of microbes that live within human's body. These microbial communities reveal substantial topographical variations and temporal intricacy, and are commonly commensal in nature. They contribute significantly to the host's genetic repository and biochemical activities, giving abilities that human cells have not required to evolve independently.

Progression in culture-independent isolation methodology, along with next-generation DNA sequencing technology, has expedited high-throughput analysis of these microbial populations. Such researches have showed that shifting in microbial compositions and diversity are considerably associated with several pathological conditions. Consequently, investigate the human microbiome had stand out as a substantial field of research in the molecular biology, immunology, and general medicine.

Despite the microbiome had been revealed to have a significant impact in shaping the host immunological responses, affecting metabolism, along with modifying drugs interaction. This review underlines the evolution of genomic technology that drives microbiome investigations, reveals how the microbiome modulating health and causing the diseases, along with discussion current challenges encounter this emerged line of investigation. Recognizing the importance of human microbiome on the micro and macro biological levels, Human Microbiome Project (HMP) has been started in 2007 with a principal objective of systematically characterization microbial populations correlating with human's body [1]. Among its basic goals were the collection of reference microbial genome sequences, the illustration of associations between microbiome changes and disease conditions, and adopting of multi-omics strategies to enrichment interpretation of data. As well, the HMP has developed novel computational tools and technologies to analyze the large-scale data, instituted centralized facilities to coordinat the data and research depots, and actively process the ethical, legal, and social considerations included in microbiome researches. In 2014, this project transformed into the second phase that include Integrative Human Microbiome Project (iHMP), which focused on the multi-dimensional analysis of host-microbiome interaction regarding the health and disease.

The human microbiota is refering to the varied groups of microorganisms that reside and interact with human body [1]. These associations may be commensalistic, mutualistic, and pathogenic in its nature. However, human microbiome is known as the collective genomics contents of microbes impeding at certain anatomical locations within human's body.

Microorganisms inhabit various body sites that including skin, mucosal surfaces, gastrointestinal tract, respiratory tract, urogenital tract, and mammary glands, which posing featured, localized ecosystems that dynamically adjust with the environmental conditions distinctive to every niche [2]. From birth, a continuous symbiotic associations is emerged between the individual and its indigenus microbial popualtion, playing crucial roles to promote health and maintain the physiological homeostasis.

Throughout the coevolutionary processes, these microorganisms have gradually adapted to their ecological surroundings within human's body, which actively shaping as well as being shaped according to their host environment [3, 5]. As results of their metabolic and molecular activities, they deem as an integral part of the host body, and contributed to the developmental, immunological, and metabolic alterations over the lifespan. It is worth noting, the human microbiome remaining in continual flux, affected by a wide range of specific factors of host like as diets, age, genetic, underlying disease, as well as the environmental exposures. However, shifting in the composition of the human (dysbiosis) microbiota may cause a life alarming diseases [2]. A stable microbiota had revealed to have a significant impact in health and wellbeing [2]. The gastrointestinal tract contains largest level of microorganisms within human's microbiome; it serves as a pivotal axis for the interactions between host and microbe.

These microbial population are playing critical roles in maintain the physiological functions, modulating immunological responses, and participating in overall health and homeostasis. Outcomes of the HMP have emphasized the potent associations between disturbances in the microbial compositions of gut (referred to as gut dysbiosis) and changes of host's immunological landscape. Such disparity had been contributed in etiology and progression of several life-threatening diseases, including various types of cancer, heart diseases, inflammatory bowel diseases, and emerged the antibiotics-resistant bacterial infection. This perception highlights the significance of maintaining a balanced gut microbiota to lessen disease risk and enhance resilience to encounter immune-related disorders [6, 7].

Microbiomes are growingly recognized as substantial contributors to human health, affecting pathways ranging from metabolism of nutrient to pathogenesis of chronic diseases. Their implication in inflammatory diseases like asthma, allergies, and rheumatoid arthritis remains a central of interest for investigation, although the exact mechanistic associations are yet to be fully illustrated. Current possibilities suggest three potential models: Firstly, the microbial assembly may shift responding to disease conditions; Secondly, the disease pathology may drive alterations in microbiome composition; or finally, the dysbiotic changes in microbiome may emerge or exacerbate disease progression. Although these uncertainties, a mounting body of evidence emphasizes the crucial role of microbiomes in a broad spectrum of disease affecting human's health. Particularly, gut microbiota have been revealed to considerably affect the nutritional health, thus influencing various processes like nutrients absorption, vitamins synthesis, and immune modifications. These findings confirm the importance of microbial ecosystems in maintaining physiological homeostasis and underscore their potential as promise therapeutic targets in both preventative and clinical settings [8]. The digestive tract of fetus is widely deemed to be disinfected prior to birth, where the first exposure to commensal microbes happens during delivery via birth canal. This initial link with maternal microbiome is considered to have a central role with long-term molding of neonatal immune system. The investigations using germ-free animal models have revealed the crucial roles of microbial colonization in developing the lymphoid system [9]. Gut-resident bacteria not only trigger immunological responses, but they also critical to maintain immune cells homeostasis [10]. Microbial-derived metabolites are essential to immune regulation, such as certain bacterial taxa like Clostridia had been demonstrated to modulate retinoic acid signaling pathway in immune cells, thus affecting the immune functions [11]. Moreover, the intestinal dysbiosis was proven to provoke promoted Th17 cell-mediated responses in murine models, proposing that variations in microbiota makeup could lead to aberrant immunological activities and cause inflammatory pathologies [12]. Gut microbiota could as well serve as biomarkers for chronic inflammatory disorders such as inflammatory bowel disease, diabetes mellitus type 2 as well asthma [13]. Gut microbiota reveal a perceptible capacity to affect patients responses to drug interventions. For instance, particular bacterial strains had been demonstrated to metabolize the Levodopa, a main therapeutic agent applied to manage of Parkinson's disease, thus lessening its bioavailability and potentially causing adverse impacts. Besides, gut bacteria have the capacity to modify host metabolic pathways via enzymatic suppression or transformation, which may possess clear implications for drugs performance and toxicity. This capacity underscores emergence prospective microbiome-targeted approaches to boost precision medications, such as the strategic modulation of microbial populations to optimize treatment responses and lessen the unwanted the side effects [14]. The microbiota that constitutes the microbiome could affect the responses for immunotherapy. Tumor cells could progress for evading host's immune system, assisting growth and metastases. Immunotherapies aim to enhance the hosts immunological responses to treat cancer [15].

3. The Humans Microbiome and Diseases

A-Cancers

The gut microbiota has an important impact in influencing host health and well-being [16]. Researches on the interplay between host and microbes revealed that these communities implicated in various biochemical activities that affect the carcinogenesis, tumors progression, along with responding to immunotherapeutic intervention [16]. A well-accepted model proposes that continual intra-abdominal

infections, extended exposure to antimicrobial medications, or both, might lead to dysbiotic conditions of gut, thus increasing the risk of colorectal cancer. Furthermore, the byproducts of microbial metabolism can change the integrity of intestinal epithelium, either boosting the carcinogenic processes or impeding tumor development [17]. Beyond colorectal cancer, it is found that intestinal microbiota had been engaged in the pathogenesis of extra-intestinal cancers, like the hepatocellular carcinoma, likely via the systemic spreading of microbial byproducts. *Helicobacter pylori* (*H. pylori*), a well-known gastric pathogen, had long been correlated with an escalated risk of gastric cancer. Recent investigations have also revealed an overrepresentation of *Fusobacterium* and *Clostridium* spp. in the gastric tissues of cancer patients [18]. Regarding to breast cancer, while the host genetics and environment exposures are major reasons for the disease progression, the microbial impacts have also acquired attention. Breast tissues from affected women tend to have higher assemblies of *Bacillus* and *Staphylococcus* spp. compared with healthy subjects. Moreover, *Escherichia coli* (*E. coli*) and *Staphylococcus epidermidis* isolated from cancerous breast tissues were demonstrated to cause double-stranded DNA breaks in HeLa cells. Conversely, *Lactobacillus*, which are typically related with useful health outcomes, seem to be absent in breast microbiome of affected women [19]. Similarly, prostate cancer was related to dysbiosis, with heightened profusion of *Bacteroides massiliensis* found in affected patients. Overall, changes in the microbial makeup and activities have implicated in rising consideration of the complex and multifaceted association between the human microbiome and pathophysiology of various types of cancer [18].

B- Inflammatory Bowel Disease

Inflammatory Bowel Disease is closely related with gathering of pathogenic microbes, which trigger aberrant immunological responses against tissues of host [20]. This immune dysregulation is contributed to onset of autoimmune diseases, chronic intestinal inflammations, and other life-threatening disorders. Throughout the coevolution, human's microbiota and immune system have preserve a dynamic equilibrium; nevertheless, disturbances in microbiota composition could obstruct this balance, impairing the immune regulation, and eventually lead to inflammatory pathology [21]. The study of Sunil *et al.* [22] revealed that changes of gut microbiome weaken the integrity of the gastrointestinal epithelial barrier in inflammatory bowel disease; where this barrier, which makeup from tightly connected epithelial cells, acts to separate tissues compartments and control the permeability of solutes.

The deterioration of the protective mucus layer can lead to damage this barrier, which can result in debilitated the cellular junctions and escalated the vulnerability to immune-interceded damage [23]. In IBD, the microbial dysbiosis is also characterized by a decrease in *Firmicutes* spp., which associated with high concentrations of proinflammatory cytokines like IL-12 and IFN- γ , and a concomitant reduce in anti-inflammatory cytokines such as IL-10 [122]. Interestingly, some helminth infections have been demonstrated to promote anti-inflammatory microbial populations, thereby lessening IBD severity in genetically susceptible murine models [23].

C- Cardiovascular Diseases

Metabolites of gut microbiota not only cause local impacts within the digestive tract but also affect systemically, influencing distant organs including the cardiovascular system. Remarkably, the producing of trimethylamine N-oxide (TMAO) by specific gut microorganisms had been engaged with pathogenesis of cardiovascular diseases (CVD) [24]. These microbes transform dietary precursors like l-carnitine, choline, and phosphatidylcholine into trimethylamine (TMA), which is later oxidised to TMAO by hepatic flavin-including monooxygenases. TMAO was found to interfere with lipids transport and enhance the releasing of pro-atherogenic molecules, thus leads to form foam cells and arterial stiffen in experimental animal models [24]. Other evidence points to a connection between the intestinal dysbiosis and elevated risk of CVD; In a clinical study of Kho and Lal, individuals were classified into groups depending on CVD risk profiles. The study showed that participants within the as high-risk group revealed notably disrupted gut microbita, suggested a possible link between varied microbiota and the onset or progression of CVD [25, 26]

D- Systemic Infections

The systemic infections could emerge from the transporting of microbes from the intestinal mucosa to extra intestinal regions in human body. This phenomenon is exceptionally consequential in immunocompromised patients, such as those who are prolonged hospitalized, exposing to surgical procedures, or undergoing trauma, where they appear increased susceptibility to invasive bacterial propagation [27]. Disruptions of gut epithelia, often triggered by antibiotics overusing or mucosal injuries, weakened the structural and immunological integrities of the intestinal barriers. Such disturbances boost the propagation of facultative anaerobic bacteria and diminish host immunological defenses, thus facilitating microbial translocations.

Best known pathogens engaged in this process include *E. coli*, *Klebsiella pneumoniae*, *Enterobacter* spp., *Proteus mirabilis*, *Enterococcus* spp., *Streptococcus* spp., as well as *Candida albicans* [27].

Additionally, microbial transportations contribute to systemic pathology via producing the uremic toxins. Dysbiosis-triggered syntheses of nitrogenous compounds are undermining epithelial narrow junctions, permitting for microbes and their metabolites to invade systemic circulation. These toxins could evoke extensive inflammatory responses and have been associated to the pathogenesis of various chronic diseases [23].

4. The Human Microbiome and Allergic conditions

Growing evidence has explained possible mechanisms by which human microbiome implicated with developing of allergic conditions [120]. While the roles of lung-resident microbiota in controlling respiratory immunity remain not fully understood [128], it is obvious that the respiratory tract is notably affected by microbiome of gut, which modulating the mucosal homeostasis in distant sites including lungs. The microaspiration of dysbiotic gut flora may enable microbial transportation to respiratory tract, increasing the susceptibility to respiratory diseases.

Renz et al. revealed this phenomenon in germ-free murine models, which don't have functional immune regulatory network, therefore get respiratory and allergic conditions [129]. The delivery model had also been acted as a risk factor in the development of allergy. Neonates delivered by cesarean section (CS) are not exposure to maternal vaginal microbiota, leading to changed gut colonization patterns and enlarged predisposition to allergic conditions [130]. Molecular analysis demonstrated that CS-delivered infants showed significantly decreased levels of beneficial bacterial genus such as *Bacteroidetes*, weakening the anti-inflammatory mechanisms and enhancing tissue-specific inflammations, such as asthma and allergic rhinitis, which driven by various genetics and environmental elements [120].

Epidemiological investigation further link the dysbiotic gut flora with increased immunoglobulin E (IgE) levels, a principle mediator of airway hypersensitivity in pediatrics populations [31]. In addition, lower microbial diversity, especially in *Bifidobacterium*, *Akkermansia*, and *Faecalibacterium* spp. has been associated with heightened susceptibility to multiple allergen sensitivities (polysensitization) and developing of asthma at age four [32].

Supporting these outcomes, Huang et al. documented that germ-free mice exhibited increasing susceptibility to allergic airway inflammations, which were notably lessened subsequent to microbial colonization. Complementary investigations across European farming populations demonstrated that exposure to microbiota-rich environment was inversely correlated with the frequency of allergic respiratory diseases [33]. The protective impacts have been assigned to innate immune activation within respiratory epithelial cell, which induced by exposure to farm dust rich with microbial spp. like *Acinetobacter lwoffii* F78 and *Lactococcus lactis* G121, both of which were revealed anti-inflammatory capacity in murine models [33, 34].

5. The Humans Microbiome in Health Sustenance

A- Maintenance of Homeostasis.

The humans microbiome has a decisive role in both maintenance and development of physiological homeostasis over the life. These microbial populations are influential in the starting and modulation of immune system, especially in controlling the inflammatory responses and immune maturation in neonates as well as young children [22].

The study conducted by Melli indicated that children who evolved allergies later in life have a higher prevalence of Bacteroidaceae and anaerobic bacteria, as well as decreased populations of useful microbes like *Bifidobacterium adolescentis*, *Bifidobacterium bifidum*, and *Lactobacillus* spp. [34]. Further research has proven that the microbiome actively reacts with and degrades environmental contaminants like heavy metals, polycyclic aromatic hydrocarbons, pesticide, ochratoxin, plastic monomers, and different organic pollutants, thus contributes to detoxification process within the body [35]. Subsequent to renal filtration, the toxins eliminated from circulation were accumulated in bladder, forming an appropriate environment for urinary tract microbes to metabolize and disrupt the toxic substances [36]. This microbial activity is closely related to infections outcomes and immunological defense mechanisms. In female genital tract, the local microbial flora is playing a crucial protective role by triggering the innate immunity. This involves the production of bioactive compounds like cytokines, antimicrobial peptides, and inhibitory substance, which altogether reinforce mucosal barriers against microbial pathogenic invasion [36].

B- Development of Host Immune System.

Throughout a long history of coevolution, the indigenous human microbes and host's immune system have evolved complex mechanisms of mutual adaptations. This association enables the immune system to effectually differentiate between pathogenic organisms and those commensal ones that are needed for physiological balance [37]. Within gut, the composition and diversity of the microbiota are exceptionally impact in shaping evolution of adaptive immune system. Thereby, the mammalian immune system is intricately mold by exposing to microbes throughout the early life.

Recent investigation had revealed that an absence or early disturbance of commensal microbial communities could cause an exacerbation of type 2 immune responses, often manifest in allergic conditions due to impaired regulation of immune responses. In pediatric, changes of microbiota driven by epigenetic triggers such as cesarean section births, physical inactivity, environmental pollution, and Western-style dietary styles have been correlated with escalated prevalence of allergic rhinitis in children [30]. Several intervention strategies like probiotic supplementations, breast feeding, permitting for some outdoor games that enhance the synthesis of endogenous vitamin D, and allergen-specific have been proposed to support immune system maturation as well as the immunotherapy targeted allergen could minimize the occurrence of atopy in children [15].

A- Nutrition of Host

The microbiota of colon has significant roles in meeting the host's nutritional requirements by fermenting the complex dietary compounds that are hard to digest by intestinal epithelial cell [138]. Particularly, these microbes help to breakdown the complex carbohydrates, making nutrients more bioavailable for absorption and metabolism. Among the main metabolic products generated via microbial fermentation in the gut are the short-chain fatty acids (SCFA), including acetic acid, propionic acid, and butyric acid, which originate from the breakdown of carbohydrates and amino acids [39]. Once being absorbed by mucosa of colon, SCFA act as essential energy sources, serve as a precursor to synthesis the mucosal lipids, and enhance epithelial cells generation, thus preserve gut integrity.

Besides, this microbiota participates to cancer prevention within large intestine, primarily via the production of butyrate, a principle SCFA formed from fermenting the complex polysaccharides. Butyrate displays anti-carcinogenic characteristics and boosts colonic health by controlling inflammations and maintaining epithelial barriers functions [39]. Remarkably, the comparative researches have

demonstrated higher levels of *Bacteroidetes* and SCFA in stool specimens of African mothers and babies, comparative to their European counterparts. These variations are mostly due to dietary dissimilarities, because the Western-style diet of European populations tends to have lower in SCFA-boosting substrates [39]. Investigations were shown that the consumption of traditional and fermentable carbohydrate may have contributed to the prevalence of healthy gut microbiome [26].

Another significant role for colonic microbes is the providing of vitamins requisite for host development. Some gut bacteria like *Bifidobacterium* spp., *Bacteroides* spp., and *enterobacteria* are accountable for producing of vitamins [37]. For instance, Vitamin K is a crucial coenzyme required to synthesis a number of clotting factors which involve prothrombin (its insufficiency leading to detain blood clotting and uncontrolled bleeding). As well, folic acid is a key precursor to synthesis DNA and RNA; they also being required to synthesis of erythrocytes and leukocytes [40]. Currently, probiotics contain lactobacillus or Bifidobacterium are utilized to treat the allergic disorders.

Outcomes for usage the probiotics as treatment possibility had demonstrated that a boosted immunomodulatory impact is conducted by lessening or inhibiting antigen-inducing T-cell activation and by prohibiting cells signaling protein (tumor necrosis factor) implicated in the systemic inflammations [41].

6. Functions of the Microbiome

The microbiome plays a role in supporting and maintaining the body's health, including stimulating the immune system, aiding in food digestion, and producing essential nutrients such as vitamins. [3] These are explained below:

A-Supporting Skin Health

Microbes live on the surface of the skin, within pores, sweat glands, and around hair roots, helping to protect it from pathogenic germs and maintain its health. Therefore, it is believed that any imbalance in these microorganisms may cause many skin problems, such as acne, eczema, psoriasis, and others. [4][5]

B-Enhancing Digestion

The gut is the largest and most diverse home for the microbiome in the human body, which plays a role in food digestion, affects the effectiveness of some medications, and aids in the production of vitamins [4]. An imbalance in the gut microbiome can lead to various health problems, such as inflammatory bowel disease, irritable bowel syndrome, Crohn's disease, celiac disease, and others. It is also believed to be linked to obesity and some chronic diseases, especially type 2 diabetes [4].

C-Maintaining Vaginal Health

The vaginal microbiome relies primarily on lactobacillus bacteria, which produce lactic acid. Therefore, the vaginal pH is low (around 4), which reduces the growth of harmful bacteria and thus prevents vaginal infections (fungal or bacterial). [5]

E-Enhancing Brain Function

Studies have shown that the gut microbiome may influence sleep and mood, as it is believed to produce neurotransmitters, such as serotonin and dopamine, which are chemicals that transmit nerve signals between brain cells and influence mood and psyche [4][6][7].

Therefore, it is believed that an imbalance of beneficial microbes in the intestine increases risks of psychological conditions, such as anxiety and depression, and even brain-related diseases such as Alzheimer's. However, these findings are still preliminary, and further studies are needed to confirm their validity. [6][7]

F-Immune System Support

We often hear that the first years of a child's life are the most important period for immune system

development. During this time, the body is exposed to various types of microbes and bacteria, which help build a strong and balanced immune system, reducing the child's likelihood of developing allergies, asthma, and autoimmune diseases in the future. [8]

G-Maintaining Oral Health

The oral microbiome lives in areas such as the surface of the teeth, tongue, cheeks, and gums, and promotes oral and dental health. However, it is important to maintain good dental hygiene, as some types of bacteria convert sugars in food residues into acids, which can cause enamel erosion, cavities, and gum disease. [4]

7. Factors Affecting the Microbiome

The microbiome does not remain constant. Rather, the type of microorganisms may change, increasing or decreasing depending on the following factors: [9][7]

A-Genetics

It is believed that these genes determine the diversity of the body's microbiome.

B-Method of delivery and breastfeeding

Babies born vaginally acquire their mother's microbes from the vagina, while babies born by cesarean section are exposed to skin microbes. Breastfeeding also plays a role in shaping the baby's microbiome.

C-Diet

Some nutrients, such as fiber, nourish beneficial bacteria and promote their growth, while processed foods, sugars, and harmful fats may reduce beneficial bacteria and stimulate the growth of harmful species.

D-Environmental factors

The microbiome is affected by personal hygiene, exposure to pollution, disease, and physical activity levels, among other factors.

E-Medications

For example, antibiotics greatly affect the balance of the microbiome. While they kill harmful bacteria, they can also eliminate beneficial bacteria, especially when used for long periods without consulting a doctor.

F-Age

At birth, our microbiome is less numerous and diverse, but this changes with age.

G-Weight changes

The microbiome is affected by weight gain or loss. A study has shown that overweight people have unique microorganisms that help store body fat. This may be linked to an overeating of fats, sugars, and carbohydrates.

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