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Roles of Gut Microbiota and Human Diseases

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Abstract:

The symbiotic relationship between gut microbiota community and its host has brought about numerous health benefits involving the immune system and homeostasis regulation. In this literature review, a crosstalk on the wide range of health benefits resulting from the complex linkage system between commensal microbiota community and gut intestinal tract including production of essential molecules, and bile acid and lipid metabolism are highlighted. Various molecular phytochemicals and its influence on growth of certain microbe strains as probiotics is discussed. Examples of chronic diseases such as Inflammatory Bowel Disease, colitis, and Colorectal Cancer resuting from gut microbial dysregulation are in regards to influential external factors like alterations in lifestyle, diet patterns, circadian rhythms, and antibiotics. Altered microbial population associates with tumorigenesis and cancer development at immune checkpoint inhibitors as well as resistance against chemotherapeutic drugs. Benefits of maintaining a balanced and healthy microbiota community wil provide insight of a potential alternative natural prevention against numerous diseases and promoting an overall healthy wellbeing. Nevertheless, many challenges and limitations remain in studying more about the host-microbiota interaction. This review aimed to highlight how gut microbiota involve in serviral diseases in which this review suggested that the gut microbiota may be able a solution an serves as a substitute for conventional medicinal therapies as an natural alternative.

Keywords **—gut microbiota, immune system, homeostasis reguation, phytochemicals, chronic diseases, tumorigenesis**

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I. INTRODUCTION

Microbiome refers to the genomes of diverse microbes within a community or environment, whereas the term microbiota is defined as the microbes themselves in aggregate (Bull & Plummer, 2014; Rath & Dorrestein, 2012). Trillions of these microorganisms, mostly being bacteria, colonize on various sites of the human body ranging from the skin to mucosal surfaces as well as the gastrointestinal tract (Beaumont et al., 2016; Le Roy et al., 2018). More than a 100 trillion symbiotic bacteria exist within the human intestine which together constitutes the intestinal flora (Haque & Haque, 2017; Hooper, 2009; Scarpellini et al., 2021). With its numerous uncountable genes, the microbiome substitutes the host's functions thus influencing over the host's phenotype and health in areas such as immunity, metabolism, intestinal tract integrity, nutritional responses, and resistivity against foreign pathogens (Hacquard et al., 2015; Lynch & Hsiao, 2019; Yin et al., 2019). This review aimed to hightlight the benefit of microbiota on human diseases regarding irritable bowel disease, infammation and cancer as well as the relationship between gut microbiota and immune responses.

II. IIRITABLE BOWEL SYNDROME (IBS) AND GUT MICROBIOTA

The human intestinal microbiome and inflammation-related diseases have been extensively investigated in recent years, and it has been discovered that microbial profiles are the consequence of the gut microbiota-metabolites interaction, which are varied and reliant on the individual's chronic diseases (1, 2). Inflammatory Bowel Disease (IBD) is induced by microbial dysregulation and instability as well as reduced commensal bacterial diversity due to excessive immune response towards pathogens (3). The two major types of IBD are identified as Ulcerative colitis (UC) and Crohn's disease (CD) (4). Ulcerative colitis (UC) is identified as a simultaneous colon inflammation due to commensal bacteria diversity declination, microbiota instability, and adverse effects from therapies and drugs in comparison with normal gut microbiota (5, 6). Particular species of bacteria like the phyla Firmicutes and Bacteroidetes experience immense depletion in UC patient's gut microbiota, expressing abnormality in the bacterial community(7, 8). Meanwhile, phyla Actinobacteria and Proteobacteria exhibit an increased abundance despite having the overall bacterial diversity decreased in other clinical reports on UC patients (9, 10). Isolation of certain species like *Fusobacterium varium*, *Fusobacterium nucleatum*, and *Escherichia coli* from UC patients were carried out, believing they were responsible for inducing intestinal chronic inflammation (11-14). On the other hand, CD exhibits both mixed healthy and inflamed regions throughout the entire GI tract (15, 16). CD patients are found with reduced abundance of genera Faecalibacterium and Roseburia while Escherichia Coli and *Ruminococcus canvas* increased in levels (17-19). Overall, IBD initiates from the dysfunctional gut microbiota-host interaction-induced mucosal immune response and intestinal chronic inflammation which eventually leads to a declined gut bacterial diversity and dysregulation of commensal microbial (2, 20). High potential in restoring gut microbiota homeostasis as well as prevention of IBD reoccurence is revealed through dietary intervention (21).

Gut Microbiota, Obesity, and Metabolic Syndrome

Defined as body mass index (BMI) of value greater than 30 kg/m^2 obesity is characterized by the bodily accumulation of lipid and excessive productions of proinflammatory adipokines by adipocytes and macrophages (22-24). Together with resistance against insulin, obesity may potentially develop metabolic syndromes such as high blood pressure, high-blood glucose levels, low high-density lipoprotein levels, high serum triglyceride levels, and large waist circumferences, which eventually can increase the individual's risk of heart disease, diabetes mellitus, and stroke (22, 25, 26). The development of the condition of obesity is not only determined by genetic changes, but also involves the major driving forces like high-caloric diet, sedentary lifestyle, and many other external prevalent in the modern generation (27, 28). Diets and various non-communicable diseases (NCDs) like obesity, metabolic syndorme, and diabetes have been identified to be associated with the human gut microbiome diversity and in numerous recent studies (29-34).

The gut microbiota also hints of its association with obesity as viewed in induced mice experiments. Through conventionalization in mice, transplant of gut microbiome from obese mice, as well as western diet-induced mice, to germ-free mice exhibit a 60% increase of adiposity composition than from lean mice which is identified through increased capacity for energy harvest, acetate and butyrate levels as well as a 50% reduction of Bacteriodetes microbial composition and increase abundance of Firmicutes (32, 35-40). Moreover, it is revealed that obese mice leaves behind less energy in their feces as tested from the fecal pellets since the mice themselves was able to extract higher efficiency of energy from their diet (29). This is most likely associated with Mollicutes, a bacterial class of the Firmicutes phylum commonly found in up-regulated by diet-induced obesity which is responsible for the increased energy

harvestation of the host(32). The bacteria enable microbial genes enrichment and KEGG pathways, providing dietary carbohydrates the process of anaerobic fermentation (41, 42). In addition, an endotoxin called lipopolysaccharides (LPS) produced on all gram-negative microbes' outer membrane trigger systemic inflammation and drives the a state of metabolic endotoxemia which ten initates obesity and insulin resistance (31, 43). In human trials, a noticeable decrease in Enterobacteriaceae feces is identified in adolescents of a 3-month diet program focusing on energy restrsction and exerting physical activity who has lost over 4-7 kg of weight (44). Furthermore, obesity and metabolism were revealed to correlate with microbiota's diurnal oscillation (45, 46). In comparison to fat-diet-induced mice with regular circadian rhythm, those whose circadian rhythm is distrubed exhibited altered microbial composition, higher weight gains and glucose tolerance (45). Furthermore, dysbiosis is exhibited in germ-free mice transplanted with jet-lagged mammal feces which leads to an increase in weight and glucose tolerance (45).

Gut Microbiota in Colorectal Inflammation and cancer diseases

Through the symbiotic relationship of the gut microbes and host's GI tract, diverse species of microorganisms populate the human colonic mucosa (47, 48). Disproportional intestinal microbiota community increases the likelihood of the colon's exposure to metabolic and inflammatory stimuli (49-51). The condition of gut microbial imbalance called dysbiosis have been found to be associated with lifestyle and external factors such as dietary patterns and sedentary behaviors, DNA mutations, inflammations, and alterations in the microbiome community (20, 52, 53). *Helicobacter pylori* infection, as revealed through human clinical studies, is associated with approximately 50% higher chance of developing CRC (54-56). As high as 46.1% of *Helicobacter pylori* is found in CRC cases in a German case-control study in from 2003-2007 as compared to those in the healthy control group which is only 40.1%. Firmicutes is one of the most prevalent gram-positive phyla in the human colon microbiome (57, 58). Firmicutes accounted for 43.46% of overall gut mucosa Firmicutes in healthy people and 63.46% in CRC patients (59). However, Firmicutes in tumors' mucosal tissue are found at 37.12%, lower when compared to regular mucosa at 44.72% as shown in another human clinical study (60). A gram-negative bacteria like Fusobacterium is found more extensively in CRC individuals than the healthy group of mice and humans (61, 62). A significant increase of 0.03% to 10.58% Fusobacteria abundance in the gut microbiota of CRC patients from healthy individuals is observed (59). The given evidence suggests the accumulation of these microbiota species during the colorectal carcinogenesis. Prognosis of colon carcinogenesis is suggested to be strongly dependent on inflammatory and metabolic stimuli as well as the microbial community structure. Suggestion of potential research in areas of GI microbiota and the associated modulatory cellular pathways remains available.

Depending on its composition, the gut microbial community may have a favorable or negative impact on pathological processes such as tumorogenesis and development. Surprisingly, various microbe-derived compounds contain anti-tumor properties.

Microbial-derived SCFAs obtain potential anti-cancer effects as observed from the inhibition of the host's tumor cells histone deacetylases with a general anti-cancer activity by the gut bacterial butyrate and propionate (63). This exemplifies the antitumor mechanism of butyrate exhibited in both colorectal cancer (CRC) and lymphoma (64). Certain probiotics-derived molecules and metabolites contain characteristics of modulating the host's immune system, prompting an collateral immune-mediated response against tumor development (65). For instance, a vital component of the in gram-negative bacteria's outer membrane categorize a bacterial lipopolysaccharide (LPS) initiate the host's cell surface receptor toll-like receptor 4 (TLR4), which belongs to the pattern recognition receptors (PRRs) family, thus triggering immune T cell-mediated response against cancer cells (66-69). Furthermore, pyridoxine, a group B

vitamin derived from bacteria, has the ability to stimulate the host's antitumor immune surveillance properties (70). Various commensal bacteria provide their host myriad health benefits through their probiotic role, like gut dysbiosis protection and the host's immune defense mechanisms enhancement (62, 71-73). Anti-inflammatory activity is observed in a rat model with inflammatory bowel disease through enhancing intestinal antibiotic rifaximin with administered Mutaflor probiotics (74). In addition, potential antineoplastic activity is evident in many probiotics, for instance mice administeered with probiotics-derived metabolites exhibit inhibition of tumour growth. Such example can be seen in ferrichrome metabolite obtained from secretion of *Lactobacillus casei,* which has the ability to trigger apoptosis of tumour cellsvia direct activation of JNK pathway (75, 76). Furthermore, Lactobacilli is revealed in several studies of its ability to trigger host's immune cells such as dendritic cells (DC) NK cells, or TH1 response, leading to the inhibition and eradication of precancerous or cancerous tumour cells. However, the mechanism of bacterial bioproduct mediating like stimulatory effects remains for further identification (77, 78).

Meanwhile, infectious strains can potentially affect the host oncogenesis indirectly via meditative process. Oxidative stress can potentially induce cell autonomous genomic mutations while inflammatory enhancement or response of host's immunity inhibition assists the immune evasive tumors (65, 79-81). The ability to initiate the host's spermine oxidase evident in *Helicobacter pylori* and *Bacteroides fragilis* produces hydrogen peroxide and reactive oxygen species (ROS)-induced accumulation of DNA damage (82, 83). Once diffused into the cells, extracellular superoxide and derivative oxygen species produced by *Enterococcus faecalis* are revealed to enhance the host's possibility of cellular DNA mutations (84).

In addition, stimulation of carcinogenesis via blocking immune-effectors typically involved in the tumorigenesis inhibition process is influenced by relevant bacteria species such as *Fusobacterium nucleatum,* which inhibits natural killer cells (NK) to allocate myeloid suppressor cells to the infectious region, indirectly assisting cancer genesis (85). This mechanism made possible through the ability to bind and inhibit NK inhibitory receptor TGIT of bacterial virulence factor Fap2, thereby detaining the NK-mediated tumor cell attack (85). Specific microbiota strains are revealed to potentially interfere with the hormonal metabolism of host which has been associated between bacterial secretion of β-glucuronidase enzymes and the increased availability of estrogen hormones in host, from both hepatic catabolism and phytoestrogens. Intestinal dysbiosis with an increase of β-glucuronidase-secreting bacterial population, such as *Clostridium leptum* and *Clostridium coccoides*, induces deconjugation liver-catabolized and plant-derived estrogens via enzymes, thus allowing them to attach and initiate estrogen receptors expressed by target cells (86). These activated estrogen receptors then promote growth of estrogen-responding tissues such as the endometrium and breast (87). Correspondingly, estrogen hormone consumption correlates with an increased risk of breast cancer development. This explanation supports finding the varied gut microbiota composition of female breast cancer patients compared to the healthy control group, thereby suggesting a linkage between breast cancer development and over-expressed gut bacteria in times of microbiome dysbiosis (88).

Despite the various findings of pathogenic microbiota's capability of oncogenesis promotion via modulation of cellular pathways of oncogenic host or interference with the endocrine or immune system, there has been no specific identification of strong bacterial oncogenic promoters. Furthermore, it is difficult to precisely explain the cancer genesis ability or the contrary of microbiota alteration (89). In addition, there exist numerous influential factors on the microbiota composition and activity, such as changes in lifestyle, diet, and immune system (90). Specific anti-cancer treatments may also alter the patient's microbiome, which can profoundly affect a patient's response to the therapy.

Gut microbiota and immune systems

The early-life colonization on mucosal surfaces of mammals has a significant impact on the host's immune system maturity progress (91, 92). Tthe maturation process initiates from the highly variable microbiota composition during the first years of life before stabilizing the adult-like configuration at approximately 3 years of age (93-95). Nonetheless, the process of development and habitizing of these microbes may increase the infants' susceptibility to environmental incursions, which can pose long-lasting adverse impacts on their immunity (96). Newborns and infants' immatured immune system is exemplified by their heightened sensitivity to a variety of pathogenic microbes, thus increasing their rate of infectious disease and eventually influencing upon child's mortality (97, 98). Prematurely born newborns, on the other hand, have a higher proclivity for severe inflammation, as evident in potentially fatal condition necrotizing enterocolitis (99). Recent cases, reproducible microbial colonization of those existing in the utero have not been identified, which is understood by the fact that the majority of colonization occurs after birth, with the majority of colonization coming from the mother microbiota (100, 101). Several external factors modulates the initial colonization progress such as delivery mode which is influential upon the initial microbiota composition across bodily surfaces (102). Studies have reveal neonates maternal antibodies obtaining passive protection capabilities against pathogen from which is gained through breastmilk (103). Recent work provides evidence of antibody-mediated protective immunity driven by commensal microbiota composition in pregnant mice through breastfeeding (104).

In studies of germ-free (GF) animals, the lack of beneficial microbes is revealed to be influential upon severe dysregulation and altered in lymphoid tissue structure and immunological function in the intestine (105). GF mice display a significant reduction of αβ and γδ intra-epithelial lymphocytes (IELs) in comparison to conventional colonized animals, which can be induced upon de novo colonization (106). IgA antibodies, which are a vital component of protective humoral mucosal immunity, are significantly reduced in infants and germ-free animals but are recovered by colonization of commensal community rapidly (107). Th17 cells like IL-17+CD4+ T cells, often abundantly present in the small intestine's lamina propria, which serves as potent immunomodulatory effector cells, are revealed to be absent in GF mice and are generated by colonization commensal microbes, more specifically segmented filamentous bacteria (SFB) as well as other commensal bacteria (107-109). Commensal microbes' extracellular signals influence gut immunoglobulin repertoires and regulate the early B cell lineage in the intestinal mucosa (110). The establishment of an immunoregulatory network that guards against the production of mucosal IgE, which is connected to allergy sensitivity, is dependent upon early-life intestinal microbial diversity (111). Toll-like receptor 5 (TLR5) is an innate immune receptor that acts as a bacterial flagellin receptor. Although TLR5-mediated colonizing flagellated bacteria counter-selection is restricted to the early years of mice, this essential mechanism alters gut microbiota configuration and affects immunological homeostasis and health in adults (112).

II. CONCLUSIONS

In conclusion, the host immune-microbiota interactions initiate in the early years of life. They have brought about long-lasting impacts on the immune system and homeostasis and influence the host's vulnerability to infections and inflmmation-realted diseases in the progressive life stages. However, the interaction mechanisms remain ambiguous. Thus future research in humans is required to accurately identify the long-term effects of dysbiosis of the microbiome during the infant years on mature immunity and the challenges of immune-mediated illnesses. With more detailed elaboration on the modulatory effects of the interaction between microbiota and the overall health, effective precaution and treatment of immune-related disorders can be applied to humans.

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