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Microbiota and Related Disease

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Abstract

The microbiota is a complex community of wide range of bacteria and other microorganisms that can be found in numerous parts of human body, including the gastrointestinal tract, skin, mouth, respiratory system and vaginal canal. Over 70% of the microbiota live in a mutualistic and beneficial relationship with their host. Every individual has a distinct gut microbiota composition, which play a range of roles in the food metabolic system of the host, the structural integrity of the gut mucosal barrier, immunomodulation and pathogen protection. Taxonomically there are different microorganisms categorized in the gut microbiota. Early in life, the makeup of each human intestinal microbiota is determined by the changes in infants (gestational age, delivery, dairy feeding and weaning) as well as external variables, such as the use of antibiotics. In adult life these personal and balanced cores of native microbiota are typically constant, although enterotypes, BMI levels, working-out frequency, lifestyle, cultural and nutritional habits differ from person to person. As a result, since the gut microbiota makeup of each individual is different, there is no optimal intestinal microbiota composition. However, a balanced healthy host-microorganism must be maintained in order to perform metabolic and immunological activities in an optimal manner, and avoid disease progression. There are a number of extra-intestinal disorders that lead to microbiota dysbiosis, including metabolism, neurology, and cancer. An appropriate treatment options should assist in understanding the origin and consequences of the gut microbiota balance in health and illness and also help to preserve or restore a healthy gut microbiota composition.

1 Introduction

In all mammalian vertebrates, especially humans microbiota develop from a clear environment climate, whatever the microorganisms inhabit in the various parts of the body such as "skin, oral, nasal, genital, respiratory, and alimentary tract surfaces" (Opazo *et al*., 2018). The microbiota, also known as the microbial flora or the normal flora, is a collection of microorganisms that survive peacefully with the host (Sekirov *et al*., 2010). The term of the microbiota referred to those bacteria that live on the surface of the human skin as well as inside the human body. The microbiota found or living in the human body outnumbers the human's body-related cells by about tenfold (Lu & Ni, 2015). An overall number of genes in this enormous collection of microbiomes could be hundreds of times that of human genes. Humans benefit in numerous ways from symbiosis with these nonpathogenic microorganisms. Even features that we have not acquired on our own are the collective genomes of the microbiome (Gill *et al*., 2006). Therefore, the human body is considered as a superorganism consisting of human and microbial components (Lu & Ni, 2015). When an effective microbiota composition is formed in childhood, it influences health and immunological homeostasis at maturity (Ranucci *et al*., 2017).

The human microbiota consists of over 10^{14} bacteria that live in different parts of the body, with the intestine harboring the most diverse group (Seksik and Landman, 2015). Microbiota found in gastrointestinal tract includes *Proteobacteria*, *Firmicutes*, *Bacteroidetes*, and *Actinobacteria* (Dwivedi *et al*., 2017). Many researches have been published on the effects of gut microbiota and health, ranging from childhood to old age and on metabolic diseases such as obesity and diabetes (Karlsson *et al*., 2013), inflammatory bowel diseases (IBD) (Ferreira *et al*., 2014), cancer (Zhou *et al*., 2021) and neurodegenerative diseases, such as Alzheimer's disease (AD) (Jiang *et al*., 2017), Parkinson's disease (PD)

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(Mulak & Bonaz, 2015), and Autism (Nogay & Nahikian-Nelms, 2021). Pathogens are microorganisms that are identified and destroyed by the human immune system. On the other hand, the vast majority of gut bacteria is non-pathogenic and coexists with enterocytes. The intestinal commensals largely aid in nutrition and medication metabolism, pathogen colonization prevention, and intestinal barrier function. Simultaneously, the immune system has co-evolved to work together with the healthy microbiota to combat invasive pathogenic microbes. This review aims to highlight recent findings on the relationship between the gut microbiota and related diseases.

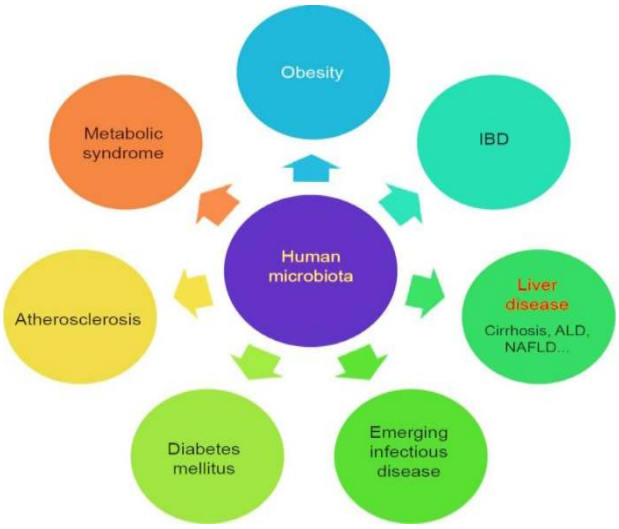

Fig-1: A complex relationship between human microbial symbiosis and disorders of multiple systems (Wang *et al*., 2017).

2 Diabetes

The human gut microbiota mainly consists of five dominant bacterial phyla include Verrucomicrobia, Actinobacteria, Proteobacteria, Firmicutes, and Bacteroidetes. The abundance of Bacteroidetes and Firmicutes are strongly associated with diabetes. Some of these bacteria have ability to produce the butyrate such as *Ruminococcus*, *Lactobacillus*, *Clostridium*, *Bacteroides*, *Prevotella*, and *Xylanibacter* when compared with the Firmicutes and Bacteroidetes phylum (Tremaroli & Bäckhed, 2012). According to human and animal studies, diabetes alters the composition of the intestinal flora. It is becoming clear that gut microbes play a role in a wide range of human disorders, including type 1 and type 2 diabetes.

Type 1 diabetes is primarily a genetic disorder, characterized by autoimmune destruction of pancreatic β-cells and environmental factors may also play a role in the pathogenesis of T1D. In recent years, the onset of T1D has been linked to changes in human lifestyle such as nutrition, hygiene, and antibiotic use, all of which may have a direct impact on the gut microbiota rather than genetic variables (Gülden *et al*., 2015) (Fig. 3).

In children the gut microbiota composition, with genetic risk of T1D and their age mater, healthy controls revealed that the risk group had a less diversified and dynamic microbiota (Murri *et al.*, 2013). In a recent study, diabetes prevention and prediction (DIPP) indicated that T1D patients have a different gut microbiota composition than controls. In the control group the lactate- and butyrate-producing bacteria promoted mucin synthesis to maintain gut integrity, whereas non-butyrate-producing lactate- utilizing bacteria inhibited mucin production, resulting in β-cell autoimmunity and T1D (Brown *et al*., 2011). Many other investigations confirmed the changes in gut microbiota composition found between T1D patients and their matched healthy controls, emphasizing the need for a better understanding of the function that these bacteria may play in the development of this disease (Yang *et al*., 2015).

The relationship between T2D and microbiota suggests that bacteria play a role in overweightness, insulin signaling, and low-grade inflammation. It has been postulated that the influence of microbiota on T2D is mediated through mechanisms including changes in the secretion of butyrate and incretins (Kaji *et al*., 2014). Qin *et al*. (2012) state that T2D patients had a moderate degree of gut microbial dysbiosis, a decrease in universal butyrate-producing bacteria, and an increase in opportunistic infections. Other research has reported similar findings, emphasizing the function of bacteria in regulating pathways by T2D like glucose homeostasis, insulin signaling, and inflammation (Tai *et al*., 2015). The gut microbiota, on the other hand, has been demonstrated to influence the synthesis of critical insulin signaling molecules such as GLP-1 and PYY via SCFA and its binding to FFAR2. These two compounds have beneficial benefits, lowering insulin resistance and β-cell functioning. An increase in *Bifidobacterium* spp. has been linked to anti-inflammatory effects via GLP2 synthesis and decreased intestinal permeability. (Baothman *et al.*, 2016). It has been claimed that the microbiota has a significant role in the generation of inflammatory cytokines such as TNF-a and IL-1. These inflammatory cytokines block insulin signaling, resulting in insulin resistance and elevated blood sugar levels (Belkaid & Hand, 2014).

Research conducted on human has also highlighted the role of physical activity, to adjust body microbiota in order to improve metabolic illnesses. Moreover, according to the clinical finding, the reduced intestinal mycetes growth, inflammation, and gut permeability by six-month endurance, resistance, and flexibility training in T2D patients, which is resulting in the healthier (functional, glycemia, anthropometric) characteristics (Pasini *et al.*, 2019).

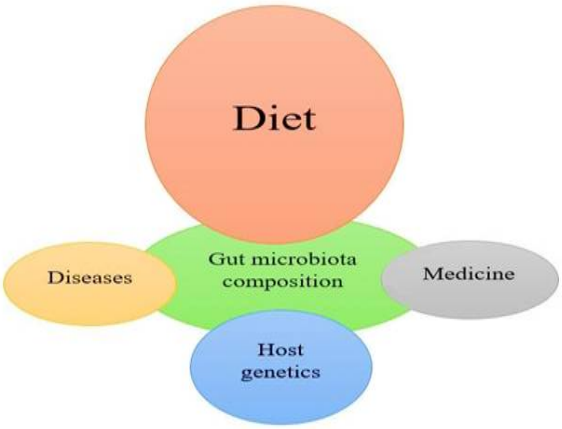

Fig-3: The composition of the gut microbiota is depicted in the diagram. Showing the importance of diet in determining this makeup and causing disruption of microbiota following causes of diseases (Zhou *et al*., 2016).

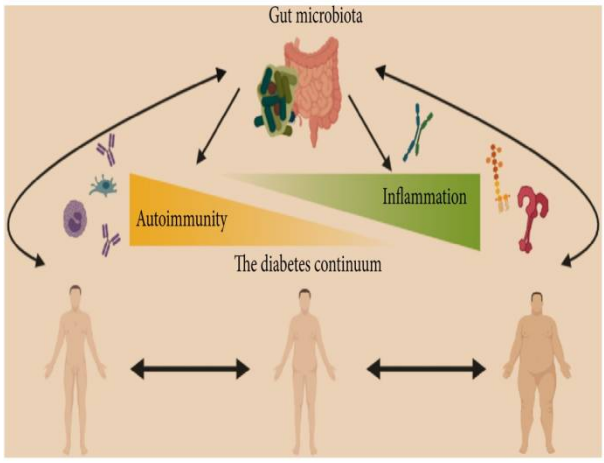

Figure 4: Autoimmunity and inflammation alterations by the gut microbiota, enhances the types of diabetes ("T1D to T2D, LADA and other intermediate forms of diabetes"). Moreover, sometime the gut microbiome changes resulting in causing structural and functional changes due to the diabetes condition (Moffa *et al*., 2019).

3 Alzheimer's Disease (AD)

Alzheimer's disease abbreviates as (AD), it is one of several in the elderly causes of dementia, a typical neurodegenerative illness, manifesting as mental diminishing. Patients have short-term memory loss, verbal memory degradation, mood fluctuations, lack of motivation, planning, and cognitive coordination skills (Mistridis *et al*., 2015). The prevalence of AD will continue to rise because the population gets older more time by time, therefore, it is increasing in closely to every country (Jiang *et al*., 2017).

A link between AD and gut microbiota has been discovered. Phylum-level of the microbiota in those who have AD condition remarks, and it is shown to decrease "Actinobacteria, Firmicutes ". On the other hand, the Bacteroidetes increase when related to standard controls groups. But there are some other less predominated in AD such as "Clostridium sensu stricto, Turicibacteraceae, Clostridiaceae, Ruminococcaceae" (Vogt *et al*., 2017).

Brain-derived neurotrophic factor (BDNF), a neurotrophin that plays a crucial role in synaptic plasticity and cognitive function, has been found to be reduced in Alzheimer's disease patients. As a result, N-Methyl-D-aspartate receptors (2A & 2B) expression by the mRNA then results in cognitive role and synaptic plasticity, which results in amygdala, cortex, hippocampus reductions. Probiotics, on the other hand, enhance cognitive function, learning, and memory while also restoring BDNF expression (Liang *et al*., 2015).

Table 1: Alzheimer's patients show change in the gut microbiota composition (Li *et al*., 2018).

Elevation microbiotas numbers	Reduced of microbiotas numbers
Bacteroidetes	Firmicutes
Proteobacteria	Ruminococcaceae
Bacteroidaceae	Peptostreptococcaceae
Bacteroides	Mogibacteriaceae
Gemella	Erysipdotrichaceae CC115
Blautia	Dialister
Bilophila	Actinobacteria
Gemellaceae	Turicibacteraceae
Rikenellaceae	Clostridiaceae
Phascolarctobacterium	Bifidobacteriaceae
Alistipes	Clostridiaceae
	Turicibacter
	Adlercreutzia

4 Autism

The term of the autism spectrum disorders (ASD) defined as a person who has difficulty in social collaboration and communication. It may happen behind the developmental of brain disorders which have stereotyped performance character (Li *et al*., 2017). ASD patients frequently experience gastrointestinal (GI) issues (Wang *et al*., 2011). There are gastrointestinal symptoms like constipation, diarrhea (20%, 19% respectively), ASD among children of their natural siblings (42 vs. 23 %). Evidence suggests that there is a relationship between the human microbiota in the gut to the ASD symptoms either directly or indirectly, maybe through impacting the immune system and metabolism (De Angelis *et al*., 2015). The gut-brain axis appears to play a role in the development of ASD, according to an increasing body of research. Moreover, the brain function regulation associated with autonomic nervous systems neuroendocrine, neuroimmune, and toxins formation by macrobiotics (Grenham *et al*., 2011).

The regulation of the gastrointestinal function made by millions of neurons locate in the GIT termed as an

Enteric Nervous System (ENS). As a result, the gut is referred to as a "second brain," elevate penetrability of the intestinal in ASD condition "leaky gut," is a crucial element underpinning the links between ASD and the gut (Quigley, 2016).

References and many researches have proven that ASD animals have abnormalities inside the GI barrier, permitting toxins and bacterial merchandise to get into the circulation and influencing brain function (Hsiao *et al*., 2013). The gram-negative cell wall of bacteria consists of lipopolysaccharide (LPS), which experimentally the LPS found more significant in the serum of a person that has ASD condition when compared with a healthy individual and has a lower social behavior score (Li *et al*., 2017). Researchers discovered that both the gut barrier with the BBB was cooperated in ASD people, also increased amount of Claudine "CLDN-5, 12, 3, and MMP-9" in the ASD brain and levels of intestinal tight junction lessened "CLDN-1, OCLN, TRIC" in ASD individuals versus to controls (Fiorentino *et al*., 2016). The lactulose:mannitol test has been shown to enhance intestinal permeability in autistic children compared to healthy controls.

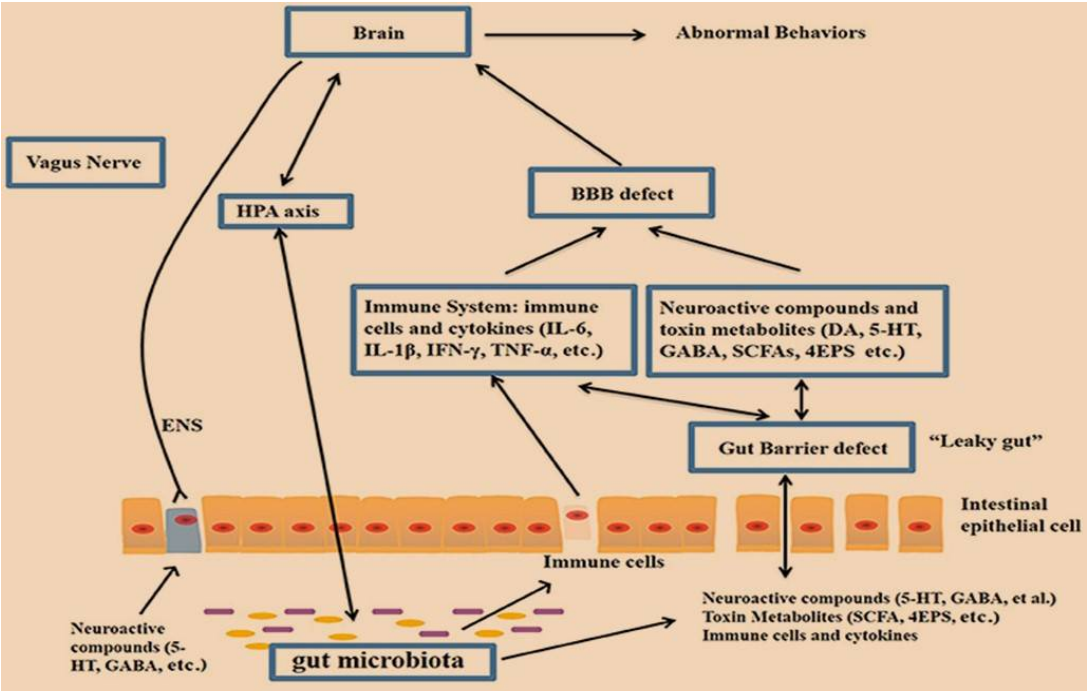

Fig-7: A possible connection of ASD with the microbiota (the gut-brain axis). Certain microbiota (e.g., Lactobacillus) can cross the "leaky intestine" and affect brain function by producing of toxin metabolites and SCFAs. Also, there are some types of microbiotas may develop neuroactive compounds such as "5-HT and GABA" and cross the "leaky intestine" which affects normal function of the brain. Moreover, compounds were involved in activation of the neurons and have the ability to stimulate the HPA axis and raise cortisol levels in the bloodstream. Via the vagus nerve, activation of neuron compounds, microbiota and metabolites can stimulate neurons behaviors which can lead to functional encouragement of the brain. Gut immune cells can be activated by microbiota and metabolites, which then release cytokines into the bloodstream. 4-EPS stands for 4-ethylphenyl sulfate; 5-HT stands for serotonin; HPA stands for hypothalamic–pituitary–adrenal; SCFAs stands for short-chain fatty acids; BBB stands for blood-brain barrier; 5-HT stands for 5-hydroxytryptamine; ENS stands for enteric nervous system; GABA stands for aminobutyric acid; DA stands for dopamine (Li *et al*., 2017).

Table 2: Alterations of gut microbiota found in autism (Mangiola *et al*., 2016).

Disease	Microbiota alterations
Autism	Imbalance of *Bacteroidetes/Firmicutes* ratio Increase of *Bacteroidetes* phylum, *Bifidobacterium*, *Lactobacillus*, *Sutterella*, *Prevotella*, *Ruminococcus* genera, *Alcaligenaceae* family

5 Parkinson's Disease (PD)

Parkinson's disease condition is associated with a long-term progressive disorder in the central nervous system (CNS) that mainly affects the motor system that leads to the widespread systemic neurodegenerative, sometime conditions characterized by a variety of motor and non-motor symptoms called Parkinson's disease (PD), now it is clear that the disease is multifactorial, impacting a wide range of functions including signaling of the endocrine system, memory actions, autonomic control, movement of gastrointestinal tract, and pain perception, etc. (Fitzgerald *et al*., 2019). Patients suffering from PD have symptoms such as tremor rest, bradykinesia, stiffness and irregularities in the gait (Shen *et al*., 2021), and a resting tremor that makes routine actions like shoes tying or computer keyboard typing difficult for patients. In addition to non-motor symptoms, hyposmia, sleep disorders, depression and dysfunction of the GIT, fatigue, olfactory dysfunction, psychiatric disorders, and mood complaints are possible diseases which is a sexual symptom (Sun & Shen, 2018). By the time patients notice motor symptoms, the disease has typically progressed, and a progressive loss in function is frequently the result. Recent research indicates gastrointestinal dysfunction may well manifest around 20 years in advance of neurological abnormalities behind the non-motor symptoms, which is referred to the prodromal phase of PD (Bridi & Hirth, 2018).

Neurodegenerative alterations characterize PD clinically in addition to the neuropathologically issue. Moreover, persons with this condition experience gastrointestinal issues, which are considered to be one of the most prominent clinical indicators of Parkinson's (Mulak & Bonaz, 2015). There is some research study that clarify that there are disruption of the brain-gut axis plays a significant role in the etiology of PD (Zhu et. al., 2017), in addition changes intestinal absorptivity behind to the epithelial barrier damages this case termed as gut dysbiosis that has an impact on the immune system (Galland, 2014). The pathophysiology of PD is caused by the basal ganglia, which are part of the prevertebral autonomic nervous system in the brain of the spinal cord. Furthermore, intestinal inflammation may cause α-synuclein misfolding, which is important in the development of PD. Inflammation of the gastrointestinal system can indeed result in brain inflammation and damage to dopaminergic neurons (Devos *et al*., 2013).

6 Inflammatory Bowel Diseases (IBD)

In Europe and the United States, the prevalence of inflammatory bowel disease is higher than in Asia (Prideaux *et al*., 2012). It is a chronic and relapsing intestinal inflammation problem that is mostly described as ulcerative colitis (UC) or Crohn's disease (CD). Although the cause of IBD is unknown, genetics is thought to play a role in the pathophysiology of the disease because a number of disease susceptibility genes have been found. The rapid increase in the incidence of IBD cannot be explained solely by hereditary factors, environmental variables also play a significant role in its development. The role of microbiota in the pathophysiology of IBD has recently been recognized. Several lines of evidence suggest that the gut microbiota play an important role in intestinal inflammation (Matsuoka & Kanai, 2015). Moreover, several alleles found in ulcerative colitis and Crohn's disease have been identified through genetic screening. However, the global prevalence of IBD is increasing, indicating that the disease is not primarily a hereditary disorder. In addition to genetic variables, environmental variables are also related to IBD. Some environmental factors that are frequently reported as predisposing factors to inflammatory bowel disease include stress, diet, infection, and tobacco. All of these factors are associated with dysbiosis, which may explain the prevalence of IBD.

On several occasions, the gut microbiota has been implicated in the development of IBD. Several studies suggest that the composition of the intestinal flora of IBD patients is significantly different when compared to healthy people, such as phylogenetic diversity, and it is the comparative abundance of the microbial class (Dicksved *et al*., 2008). Both the UC and CD gut microbiota exhibit lower taxonomic diversity, as well as increased abundance in the phyla Proteobacteria, and decreased abundance of the phyla Firmicutes. The number of bacteria in the Clostridia family is also commonly altered in IBD patients, with a decrease in *Roseburia* and *Faecalibacterium* and an increase in the *Ruminococcus* and Enterobacteriaceae family observed (Nishino *et al*., 2018). Evidence indicates that IBD is caused by aberrant immune response triggered by altered gut flora. Cytokine investigations in a murine colitis in mice revealed that *Faecalibacterium prausnitzii* had anti-inflammatory properties (Martín *et al*., 2014). IBD may be caused by a decrease in bacterial anti-inflammatory activity rather than by aggressive bacteria.

The interaction of the host microbiota with the host genetics (as well as environmental stressors not depicted in the picture) causes gradual inflammatory damage to the host's intestinal mucosa, which is reflected through distinct histological findings and symptomatology. Examples of host genetic deficiencies linked to IBD can be found in the top purple boxes. Anomaly findings from gut microbial communities of IBD patients are shown in the top green boxes. Examples of histopathological findings in IBD are shown in the bottom blue boxes. Symptoms shown by IBD patients are described in the light-yellow boxes at the bottom. A probable clinical path of IBD development is indicated by red arrows (Sekirov et al., 2010).

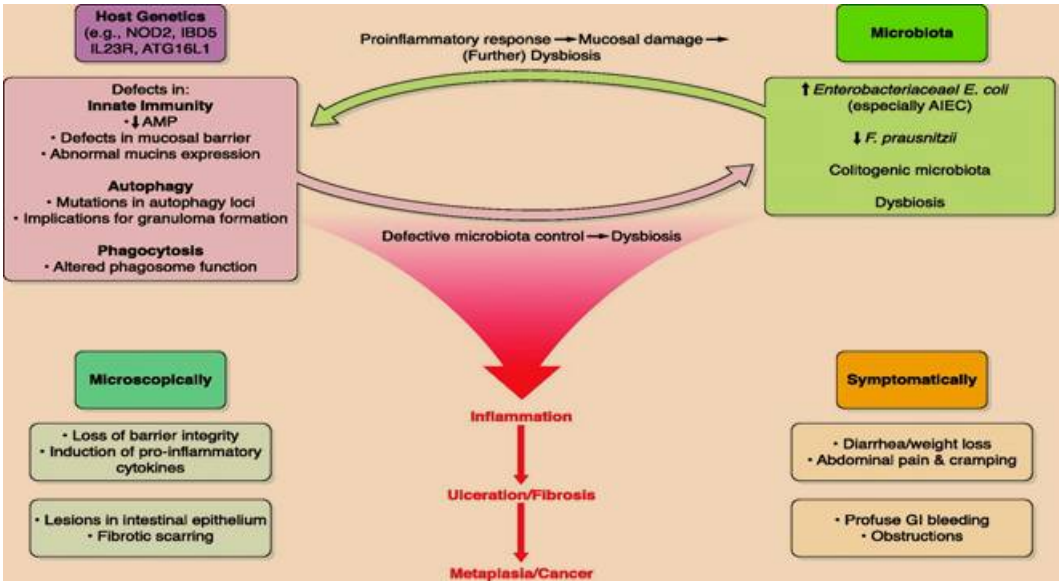

Fig-2: The microbiotas function in the pathophysiology of inflammatory bowel disease (IBD) (Sekirov *et al.*, 2010).

7 Brain

Nowadays, the relationship between the gut microbiota and brain has yet to be fully defined and clarified. In addition, these relations were not only through the neurological system (the gut-brain neuroanatomical pathway), but also through the endocrine, immunological, and metabolic systems. The gut-brain axis refers to a bidirectional connection between the gut and the brain (Wang & Wang, 2016). Many studies have found a link between changed gut flora and brain function. The brain and gut bacteria communicate bidirectionally, which is critical for brain activity and the GI tract (Zhu *et al.*, 2017). However, the mechanism of action or function of these microbiotas are not associated with the development of the central nervous system. Although, sometimes are associated with major body complication (diseases), these microbiotas in the gut influences microglia's function and maturation because the microglia are responsible for producing of some immune cells in the human body (Iadecola, 2015). Many scientists believe that changing microbiota impacts "neurobehavioral" in animal models, for example, it is linked to alterations in the brain-gut relationship (O'mahony *et al.*, 2014). Furthermore, learning, memory functions, and neurological illnesses such as Alzheimer, Parkinson's, and Autism are linked to "hippocampal neurogenesis" (Braniste *et al.*, 2014).

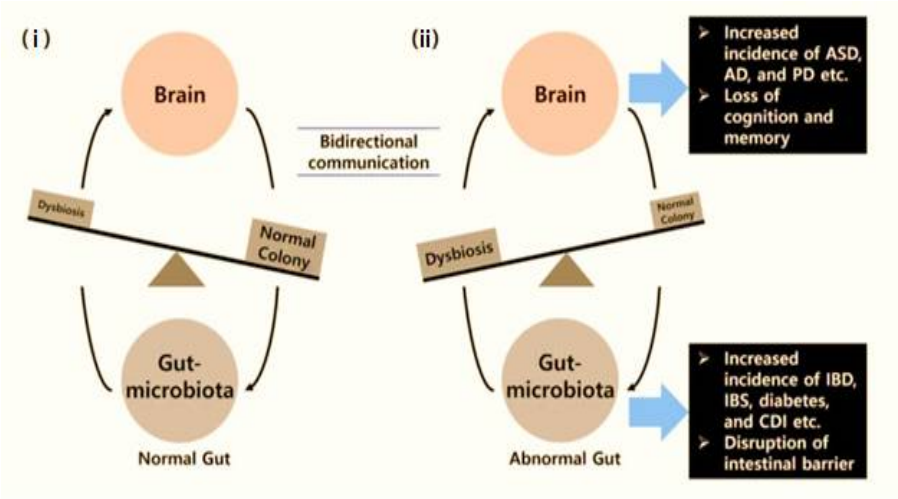

Figure 6: The gut microbiota has a bidirectional with brain (i) the brain and the gut function together through a bidirectional relationship. The vagus nerve and the intrinsic primary afferent nerve carry a signal from the gut to the brain. In various physiopathological conditions, there is a regulation relationship between the hormone messages, neurologic, and immunologic by the brain and these regulations also result in the regulation of the gut (ii) Dysbiosis in the gut microbiota is linked to a number of neurological and gastrointestinal disorders. IBD, inflammatory bowel disease, Alzheimer's, Parkinson's, and autism spectrum disorder (Choi *et al.*, 2018)

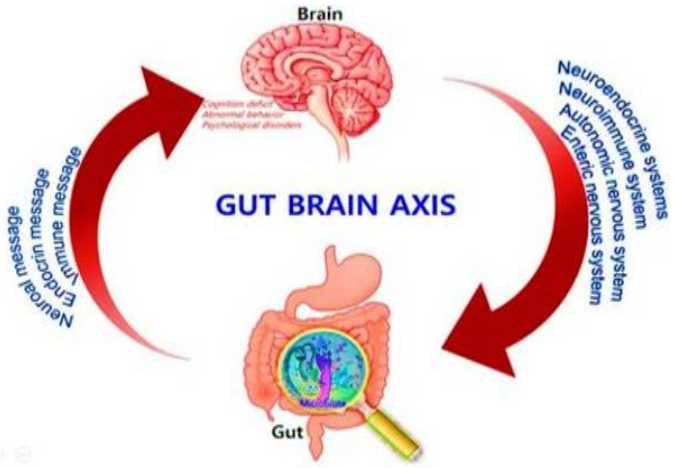

Fig-5: The neural, hormonal, and immunological stages, bidirectional communication between the gastrointestinal tract and the brain is controlled (Giau *et al*., 2018).

8 Gut Microbiota Related with Ca

The human gastrointestinal tract filled with numerous microbiotas, and it has been proven these gut microbiotas have been associated with numerous malignancies disruptions (Zitvogel *et al*., 2017), the body immunological interactions and inflammation have a role in the relations between the microbiota in the gut and cancer which are multifaceted with functioning in two directions (bidirectional).

9 Gastric Cancer

Chronic inflammation caused by *Helicobacter pylori* is thought to be the most significant risk factor for stomach cancer. *H. pylori* infection causes around 660 000 new cases of gastric cancer each year, resulting in the loss of acid-producing parietal cells, which leads to the development of gastric atrophy, metaplasia, dysplasia, and, finally, carcinoma formation (De Martel *et al*., 2012). The *H. pylori* involved with gastrointestinal tract especially stomach, if the normal condition of stomach altered by the bacteria it induces cancer in latest stages, and this type of cancer considered as a fourth maximum common cancer is the world's, *H. pylori* is microaerophilic gram-negative bacteria that produce different stomach complication with dissimilar stages that includes (chronic gastritis, peptic ulcers, mucosa-associated lymphoid tissue lymphoma, and it is categorized as a Group I carcinogen conferring to the International Agency for Research on Cancer (IARC) organization. Moreover, the *H. pylori* gastric carcinogenesis demonstrates a number of harmful pathways (Lertpiriyapong *et al*., 2014).

There are two importance virulence factors that H. pylori have such as cytotoxin-associated gene A (CagA) and vacuolating cytotoxin A (VacA), the cell proliferation, cell cycle, and cell death occurs behind to these proteins, following with transduction pathways signal of oncogene (phosphatidylinositol 3-kinase (PI3K) and mitogenic Ras-extracellular regulated kinase (ERK)) is activated. Furthermore, because the human immune system is frequently incapable of removing H. pylori, which can lead to persistent conditions in tissues with persistent oxidative stress, and resulting in DNA strand break by elevation of reactive oxygen species (ROS), behind these conditions the genomic instability takes place following subsequent carcinogenesis (Lofgren *et al*., 2011). When compared to the other regions in the gastrointestinal system, the hostile circumstances often correspond to reduce of the microbial in the stomach colonization. Nonetheless, previous investigations have shown that there are other microbiota members other than *H. pylori* that play important roles with association to the gastric carcinogenesis (Wong *et al*., 2019; Aviles-Jimenez *et al*., 2014).

10 The CRC (Colorectal Cancer)

The human gastrointestinal tract, especially the colon, is home to the greatest bacterial diverse ecosystems in the abdominal area with microbial counts, orders such as Firmicutes and Bacteroidetes dominated the bacterial population (Arumugam *et al*., 2011). Proteobacteria, Actinobacteria, Fusobacteria, and the smallest number of Verrucomicrobia are associated with the colorectum area. The connection of the gut microbiota with colon cancer development has recently become a major focus of investigation (Sanapareddy *et al*., 2012). Microbial dysbiosis has been linked to the development of colorectal adenomas and cancer (CRC). In people with adenomas, a pathogenic imbalance in the microbial population was detected when compared to normal controls (Castellarin *et al*., 2012). The colorectal microbiota, which contains a significant number of bacteria in the colorectum area, was located near the epithelium, which plays ingredients a role in established, and there is a high chance for a tumor to be developed in this part. The third development of cancer in the world involved with colorectal cancer. As a result of genetic, lifestyle, and environmental factors interacting. Heritability is thought to account for up to 35% of all colorectal cancers, with approximately 5% occurring recognized predisposition genetic disorder (Wong *et al*., 2019). These findings point to the significance of the major daily exposure which is the environment condition and the human lifestyle, these are two important factors. Moreover, there are enterotoxigenic bacteria (*Bacteroides fragilis*) with genotoxic (*Peptostreptococcus anaerobius*, *Escherichia coli*), have been shown in functional investigations to induce colorectal carcinogenesis by stimulating the Th17 cell response and producing direct DNA damage (Arthur *et al*., 2012) as well as stimulating cholesterol biosynthesis (Tsoi *et al*., 2017). Colorectal neoplasia has also been linked to clinical infections with a variety of microorganisms (Kwong *et al*., 2018).

There are numerous of bacteria such as *Porphyromonas*, *Fusobacterium*, and *Parvimonas*, *Peptostreptococcus* were involved with the colorectal area characterized by microbiota dysbiotic, which means they are able to lead to disruption to the homeostasis which caused by an imbalance in the gut microflora, and make variations in their functional metabolic activities and conformation, or a shift in their local distribution with low overall bacterial productivity and variety (Dai *et al*., 2018). *Fusobacterium nucleatum* is one of the potential bacteria associated with examination foundation amid to monitor the CRC. According to research study the *F. nucleatum* is more numerous in cancer tissues. Following, researches revealed the induce of tumorigenesis in the intestine related to the bacteria (F. nucleatum) when it is sticking to cancer cells (Abed *et al*., 2016) and immune cell modulation through protein (Fap2) (Gur *et al*., 2015).

The environment of the tumor cell could be changed by bacteria itself by promoting microRNA-21 expression as well as β-catenin cancer pathway activations (Yang *et al*., 2017). Besides, due to these above factors the bacteria can also stimulate (Toll-like receptor 4) in order to produce microRNAs dissimilar to the original one, and automotive of the pathways in addition to modify the chemical treatment responses of patients (Yu *et al*., 2017). Additionally, the resent experiment has been clarified that the Fusobacterium has a link with CRC metastasis when demonstrating the presence of viable Fusobacterium in distant metastatic lesions (Bullman *et al*., 2017).

The bacteria (Fusobacterium) have ability to tolerate to the initial tumor cells fragment of metastatic tissue occupation, following according to these findings (Bullman *et al*., 2017) it indicates the human body innate immunity system have ability to cooperate gut microbiota of gastrointestinal tract to affect the progression of extra-intestinal cancer (Rutkowski *et al*., 2015). Finally, greater Fusobacterium levels in tumors have been linked to a number of histological and clinical experiment characteristics with the proximal tumor, in addition to a decreasing number of T-cell penetration and site (Mima *et al*., 2016a), a more advanced illness stage and a lower patient survival rate (Mima *et al*., 2016b).

11 Conclusion

Every healthy human individual is born with their own set of gut bacteria. The core of the microbiota formed throughout the early stages of life, commencing with the fourth week of gestation, and other elements plays a role in this process. After a child reaches the age of 2–3 years, the composition of his or her gut microbiota remains rather stable. The richness and diversity of a gut bacteria that generated early in life describes a balanced gut microbiota composition. However, the composition of a healthy gut microbiota differs from person to person. The more complex and diverse microbiome in life, the better chance of surviving external stressors. Indeed, the gut microbiota is a dynamic ecosystem that is challenged by a range of variables such as an imbalanced diet, stress, antibiotic use, and illnesses. A good host–microorganism balance is required to perform metabolic and immunological activities properly, and to prevent disease. Disruptions in the host–microbe connection can definitely alter the development of the immune system, which can lead to aberrant states and illnesses. Despite the fact that the function of gut microbiota is yet unknown, a close relationship between the gut microbiota dysbiosis with intestinal and extra-intestinal illnesses have been revealed. As a result, dysbiosis can be exploited as a biomarker for various diseases, and conducting researches regarding gut microbiota balances will be a primary priority for future disease prevention and treatment strategies.

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