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The Role of the Gut Brain Axis and Microbiome in Colorectal Cancer, Alzheimer's Disease, and Crohn's Disease

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Abstract

The gut-brain axis consists of bidirectional communication occurring between the gastrointestinal (GI) tract and the central nervous system. This bidirectional communication is facilitated by the gut microbiome and they are involved in many everyday functions.

Communication methods include vagal nerve activation, and the production of neuropeptides, neurotransmitters, and endocrine hormones. For example, norepinephrine affects signals between bacteria and has the ability to change the microbial diversity in the GI lumen and the actions of the gut microbiome. Disruption in the communication leads to changes in intestinal motility and secretion among other things. Inflammation within the GI tract leads to an increase in the permeability of the intestinal walls creating a leaky gut environment. Inflammatory cells would then be able to cross the intestinal barrier to the blood and travel systemically reaching the brain and influencing its function.

Inflammation within the GI tract due to inflammatory bowel disease increases the likelihood of colon cancer developing. Gut microbes have the ability to control colon cancer progression by inhibiting the NF- κ B pathway and tumor necrosis factor. Dysbiosis of the gut is a key factor that induces inflammation and increases barrier permeability which promotes the release of cytokines and growth factors causing malignant transformation of colon cancer. Along with dysbiosis, obesity has also been proven to create inflammation in the gut. Animal fat and proteins such as red meat increase the risk of colorectal cancer while diets that are high in fiber decrease this risk. High-fat diets lead to increased plasma endotoxins due to increased intestinal permeability and perturbations in the microbiota within the gut. Switching to a diet that is high in fiber from a Western diet that is typically low both in fiber and high in fat causes a consequent change in the microbiota; more microbes would ferment the fiber leading to more short-chain fatty acid (SCFA) metabolites. Probiotics have become useful for the treatment of colon cancer due to its anti-inflammatory properties and their ability to decrease DNA damage and maintain the intestinal barrier.

When there is dysbiosis and inflammation in the GI tract, there is increased permeability of the gut. This allows bacteria to pass through intestinal barriers and into the blood stream where they can then access the brain. The microbial infection in the brain causes inflammation which is highly implicated in the pathogenesis of Alzheimer's disease. High levels of body fat and blood

sugar levels have been linked to the development of Alzheimer's disease. It has been shown that cardiovascular disease is an etiological hallmark of Alzheimer's disease. This further connects to the idea of type 3 diabetes with Alzheimer's disease due to the fact that Alzheimer's progresses when the brain develops resistance to insulin which allows lipids to accumulate in the brain since they are not being taken up, causing inflammation and dementia-related symptoms. Probiotics have been used for the treatment of Alzheimer's disease due to its anti-inflammatory effects and the barrier it provides to pathogenic bacteria.

Dysbiosis is the leading cause for the development of inflammatory bowel disease. The composition of the gut microbiome is imbalanced. *Proteobacteria* is a common pathogen in humans and may play an aggressor role in the development of inflammatory bowel disease. There is also an increase in *Escherichia coli* in patients with ileal Crohn's disease. Pathogenic bacteria in the GI tract leads to intestinal inflammation and increased intestinal permeability. Levels of SCFAs decrease in individuals with inflammatory bowel disease, and increase the level of sulfate-reducing bacteria, which produce hydrogen-sulfate, damaging intestinal epithelial cells and inducing inflammation. Lower levels of SCFA's mean that there are low levels of butyrate present, the main energy source of colonic epithelial cells. This is a key factor compromising the intestinal and immune homeostasis. Probiotics can restore the balance of microbes in the GI tract and enhance the intestinal barrier function. They can also reduce inflammation within the gut. Probiotics have proven very useful for the treatment of ulcerative colitis, but their effectiveness has not been evidenced in the case of Crohn's disease. This area will require further research.

Introduction

Colon cancer is one of the most commonly diagnosed and deadly cancers. In the United States, there were 140,250 patients diagnosed with colon cancer, as well as 50,630 deaths in the year 2018 alone (9). Dietary intake impacts the risk of colon cancer; diets re-shape the community structure of the gut microbiome. There has been an observed imbalance in the gut microbiome in patients with colon cancer when compared to healthy patients (10), demonstrating that gut microbiome balance is disrupted in patients with colon cancer. The underlying mechanism involves an increase in the production of metabolites that induce inflammation and proliferation, pathological bacterial adhesion, and the induction of tumorigenesis (11). Experimental evidence indicates that butyrate which is a short-chain fatty acid (SCFA) produced from the fermentation

of fiber, could suppress colon neoplasia (12). Therefore, consuming fiber could protect against colon cancer, while the consumption of red and processed meats could increase the risk of colon cancer.

Alzheimer's disease (AD) is the most common form of age-related dementia, and there are more than 5 million Americans that are currently affected with this disease. Most cases occur in people that are over the age of 65, but there are also 500,000 people who have early-onset Alzheimer's disease. 1 out of 8 people over the age of 65, and almost 1 out of every 2 people over 85 have Alzheimer's disease (14). It is the seventh leading cause of death in the United States. Recently, researchers have proposed that pathogenic microbes in the gut are involved in the pathogenesis of AD. Innate-immune and physiological barriers often become weakened with age and this allows microbes to access CNS compartments. In a study, the gut microbiome of AD patients showed a diminished microbial richness and diversity, and a distinct composition alteration when compared to healthy patients (14). This indicates that alterations in the gut microbiome in patients with AD may result in pathophysiological changes in the brain.

Crohn's disease (CD) is a type of inflammatory bowel disease (IBD) that an estimated 3 million adults in the United States are currently diagnosed with (17). The gut microbiome of patients with CD is characterized with a reduced diversity (in particular *Firmicutes* and *Bacteroidetes*). Even beyond the composition of the microbiome, the function is also different in patients with CD, which include changes in oxidative stress pathways and carbohydrate metabolism (18). Inflammation of the GI tract and other symptoms of CD are related to dysbiosis of the GI tract and it is proposed that these symptoms could be alleviated with restoration of the gut microbiome.

The common link between these three diseases is the role that the gut microbiome plays and the communication occurring with the CNS. Microbes have an important impact on the health of the GI tract and can cause inflammation which leads to the development of these diseases. As a result, this has caused probiotics to be a more popular treatment method. Probiotics are specific live microbes and can promote health in the host when consumed.

What is the gut-brain axis?

The gut-brain axis (GBA) is a network that consists of bidirectional communication between the central nervous system (CNS), enteric nervous system (ENS), autonomic nervous system, and the hypothalamic-pituitary axis. It links the emotional and cognitive centers within the brain together with intestinal functions. The role of the gut-brain axis is to monitor and integrate functions of the gut, and other mechanisms such as immune activation, intestinal permeability, enteric reflex, and enteroendocrine signaling (1). The communication between the two organ systems involves neuro-immuno-endocrine mediators.

The gut microbiome plays an important role in influencing gut-brain interactions. The importance of the gut microbiome has been demonstrated by dysbiosis in gastrointestinal (GI) disorders associated with mood disorders and a disruption in the GBA. Disruption in the GBA causes changes in intestinal motility and secretion, visceral hypersensitivity, and cellular alterations of the enteroendocrine and immune system.

It has been shown that microbiota communicate with the brain using the vagus nerve which transmits information from the luminal environment of the intestine to the CNS (3). In fact, neurochemical and behavioral effects were not observed in the vagotomized mice which indicates that the vagus nerve is the major modulatory constitutive pathway between the microbiome and brain.

There are different mechanisms through which the microbiome can interact with

the gut-brain axis (Table 1), but the main one involves modulation of the intestinal barrier, whose perturbations influence the underlying compartments (4). The microbiota can also interact with the GBA by the modulation of afferent sensory neurons and by producing molecules (Table 2) that acts as local neurotransmitters (e.g. GABA, serotonin) to influence the ENS (5).

From gut microbiota to brain: Production, expression and turnover of neurotransmitters (i.e. serotonin, GABA) and neurotrophic factor (BDNF) Protection of intestinal barrier and tight junction integrity Modulation of enteric sensory afferents Bacterial metabolites Mucosal immune regulation
From brain to gut microbiota: Alteration in mucus and biofilm production Alteration in motility Alteration of intestinal permeability Alteration in immune function

Table 1. Mechanisms involved in the communication between the gut-brain axis and the gut microbiome (1).

Gut microbiota	Metabolites product	Effects on the nervous system function
<i>Lactobacillus, Bifidobacterium</i>	GABA	Inhibitory neurotransmitter, metabolic disorders can lead to anxiety and depression
<i>Streptococcus, Escherichia, enterococci, Enterococcus, Lactococcus, Lactobacillus</i>	Serotonin	Neurotransmitters, regulate emotions
<i>Bacillus</i>	Norepinephrine	Neurotransmitters involved in motor, cognitive, memory, emotion and other central nervous and endocrine control
<i>Lactobacillus, Bacillus</i>	Acetylcholine	Acting on neurotransmitters in the central and peripheral nervous systems, and cognitive function, particularly closely related to learning and memory
<i>Lactobacillus, Lactococcus, Streptococcus, Enterococcus</i>	Histamine	Regulating neurotransmitter; sleep and cognitive function related
<i>Clostridium, C. sporogenes</i>	Indole-3-propionic acid (IPA)	Antioxidants, protect neurons

Table 2. The metabolites that can be produced by the gut microbiota and the effects that they cause on the nervous system (48).

Role of the microbiome in the gut-brain axis

The idea of the human microbiome was first introduced to the scientific community by Joshua Lederberg who defined it as the ecological community of commensal, symbiotic, and pathogenic microorganisms that share our body space and have been all but ignored as determinants of health and disease (6). The human gut contains hundreds of different bacterial species which make up an intricate network of organisms that cohabitate together. Around 10^{11} bacterial cells can be found per 1 gram of colonic contents. This is crucial because the enteric microbiota can influence our gut homeostasis by regulating bowel motility and modulating intestinal pain, immune response, and nutrient processing (7).

Inflammation within the GI tract causes stress to the microbiome by releasing cytokines and neurotransmitters. This is coupled with an increase in intestinal permeability from leaky tight junctions, allowing these molecules to travel systemically (20). When there are elevated levels of cytokines (e.g. TNF- α and MCP) in the blood, the permeability of the blood-brain barrier

increases, and the effects of these molecules that originated in the gut are enhanced (21). As a result, cytokine release can now influence brain function leading to anxiety, depression, and memory loss (22).

Intestinal microbes can alter the expression of genes in the mammalian gut mucosa, which will affect the function of the GI tract. A study was performed using germ-free and conventionally bred mice which revealed that the gut microbiome modulated the expression of many genes in the intestinal tract, including genes that involved immunity, nutrient absorption, energy metabolism, and intestinal barrier function (23).

There are many proposed pathways through which the microbiome can communicate with the gut-brain axis. One common mechanism involves the use of neuromodulators. The gut microbiome can produce numerous neuroactive molecules such as serotonin, gamma-aminobutyric acid (GABA), catecholamines, and acetylcholine which can be used to disturb the development and function of the neuroendocrine system (24). Some bacteria can convert nitrate into nitrous oxide which is a potent regulator of both the immune and nervous system (25).

Another common mechanism involves short chain fatty acids (SCFAs): butyrate has a profound effect on the enteric nervous system. Studies have shown that the systemic injection of butyrate induced histone hyperacetylation to occur in the hippocampus and frontal cortex, which exerted antidepressant effects in mice (26). Omega-3 fatty acids and propionic acid can also alter the balance of the intestinal microbiome and may be important factors.

The brain can also influence enteric commensal organisms indirectly by changing the gastrointestinal motility and secretion, and intestinal permeability, or by directly signaling molecules that are released into the lumen of the gut from cells in the lamina propria.

Communication from the enteric microbes to the host can occur via epithelial cells, receptor-mediated signaling, and through direct stimulation of host cells in the lamina propria when intestinal permeability is increased (7). Enterochromaffin cells are important bidirectional transducers that regulate communication between the gut lumen and the nervous system. Vagal innervation of enterochromaffin cells provides a direct pathway for enterochromaffin-cell signaling to neuronal circuits (28). Disruption of bidirectional communication is involved in the pathophysiology of gastrointestinal diseases.

Since the gut microbiome can alter nutrient availability and that there is a close relationship between nutrient sensing and peptide secretion by enteroendocrine cells, the interaction between the microbiome and GBA may occur through the release of biologically active peptides from enteroendocrine cells that can affect the GBA (34). Also, dietary nutrients can be converted into metabolites by intestinal microbes that then serve as biologically active molecules affecting regulatory functions in the host (34).

Inflammation and colon cancer

The gut microbiota is well-suited to influence cancer, because it has already evolved to survive and thrive in the intestinal environment (29). The microbial community can exert a collective effect to either potentiate or mitigate colorectal cancer (CRC). The development of dysplasia in colonic epithelia is strongly influenced by the inflammatory state of the colon. In the case of patients with inflammatory bowel

disease (IBD), severe inflammation increases the likelihood of developing CRC (30). As the intestinal epithelium becomes dysplastic, the barriers between the epithelium that separate the microbiome from immune cells in the lamina propria begin to degrade. This leaky gut formation facilitates bacterial translocation and the exposure of immunogenic microbial compounds to epithelial cells and antigen-presenting cells (APCs).

Inflammation causes the activation of the NF- κ B pathway, which mediates the production of proinflammatory cytokines (e.g. IL-6) that have a pathogenic role in CRC by permitting the survival and proliferation of

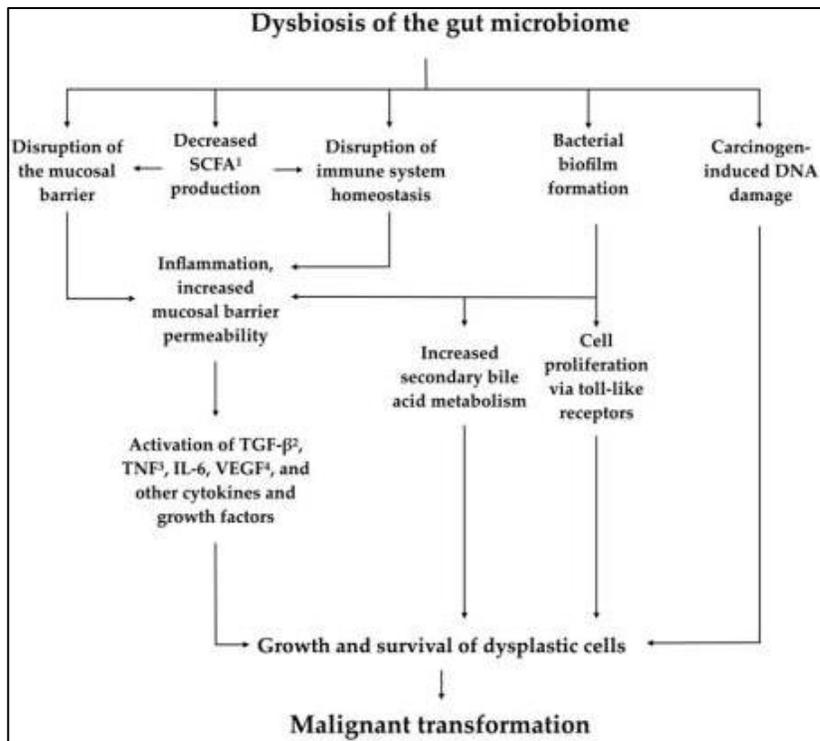


Figure 1. Pathways in which the dysbiosis of the gut microbiome leads to tumorigenesis (35).

intestinal epithelial cells. The NF-κB pathway is also an important regulator of genes that encode tumor necrosis factor (TNF) and cyclooxygenase 2 (COX-2) which are highly expressed in IBD and CRC (31). TNF acts as a positive feedback loop for the NF-κB pathway, promoting cell proliferation and survival. COX-2 is an enzyme that will produce prostaglandins and bioactive lipids that influence colonic inflammatory state and tumor progression (29). The function and development of these cells are influenced by gut microbes and their products.

Interplay between colon cancer and the gut microbiome and the effects caused by diet

Tissues with CRC have a decreased microbial diversity compared to healthy tissues. Other effects include a reduction of certain bacterial genera like *Clostridium* and *Bacteroides*, and an enrichment in *Fusobacterium* (32). This species of bacteria is found commonly in the oral cavity, but rarely in the GI tract of healthy individuals. This creates a link between this bacterial species and an inflamed colonic environment. Dysbiosis in the GI tract affects some pathways that can lead to tumorigenesis (Figure 1). Dysbiosis can cause a disruption of homeostasis in the immune system and the mucosal barrier. The result is inflammation causing an increased mucosal barrier permeability and a continuous state of inflammation. This can then activate cytokines and growth factors which leads to the growth and survival of dysplastic cells. Another pathway in which colorectal cancer can develop is through biofilm formation which leads to increased bile acid metabolism and cell proliferation which both contribute to malignant transformation (35).

Obesity is associated with an increase in intestinal permeability along with inflammation which are strong indicators that obesity exacerbates CRC (38). The occurrence of colorectal cancer

Macronutrients	Source	Influence on CRC risk
Complex carbohydrates (fiber)	Whole grains/vegetables/fruits	Decreased risk
Protein	Red meat	Increased risk
	Processed meat	Increased risk
	Fish	Probably decreased risk
	Poultry	Inconsistent, probably no influence
	Milk	Probably decreased risk
Fat	Animal fat/fatty acids	Inconsistent evidence

Table 3. Dietary factors and their influence of colorectal cancer (8).

could be reduced by 50% through diet, physical activity, and weight management. Generally, red

meat and animal fat increase the risk of colon cancer, and dietary fiber is associated with a decreased risk of colon cancer (8). Other macronutrients and their influence of colon cancer are listed in Table 3.

Increased fiber consumption has the potential to decrease CRC risk. Colonic transit is accelerated by insoluble fibers which may also lower the exposure of colonic epithelial cells to ingested carcinogens. Soluble fibers get fermented by bacteria in the gut into butyrate and other metabolites that confer benefits to the host.

Nutrients consumed by the host get converted into metabolites by intestinal microbes. Products of these biochemical conversions (e.g. short-chain fatty acids, serotonin, GABA) are biologically active in healthy as well as diseased colonic states. These metabolites also have the ability to induce changes in the microbial make-up of the gut. Dietary non-digestible carbohydrates are fermented in the intestine which results in the production of SCFAs such as acetate and butyrate. Metabolically active SCFAs are involved in biological processes that provide energy sources for colonic epithelial cells. A one-month study was performed where healthy volunteers were subjected to a high-fat, western-diet. The researchers observed that consuming a diet enriched with fat affects the intestinal microbiome (8). Plasma endotoxin levels were increased in volunteers who ate a high fat diet as compared to those with a regular diet, which may result in perturbations in the gut microbiome (34). Native Africans have a low risk of developing CRC consume a traditional high-fiber diet, whereas African Americans are at high risk of developing CRC and consume a lower-fiber Western-type diet. A study was done in which native Africans switched to a low-fiber Western diet, and African Americans switched to a high-fiber traditional diet. The results observed that the dietary changes affected the gut microbiome which led to changes in the metabolites such as SCFAs including butyrate and mucosal biomarkers of cancer risk (39). Short-term dietary interventions tend to have transient effects on the gut microbiome and are usually not maintained following a return to the long-term diet. Therefore, short-term dietary interventions will not be able to reshape the microbiome in a stable manner for CRC prevention, but rather, is something that must be done on a long-term basis.

Nevertheless, our gut microbiome does still respond to short term dietary changes. Switching from a traditional diet that is high in plant polysaccharides (i.e. fiber) and low in fat and processed sugars to a diet that is low in plant polysaccharides and high in animal fat and sugar

leads to a rapid shift in the microbiome (44). When converting to a Western diet, there is a resulting increase in bile-tolerant bacteria such as *Bilophila* and *Bacteroides* along with a decline in *Firmicutes* that play a role in metabolizing plant polysaccharides (44).

Probiotic treatment of colon cancer

Since the microbiome plays an important role in the development of cancer, the manipulation of the

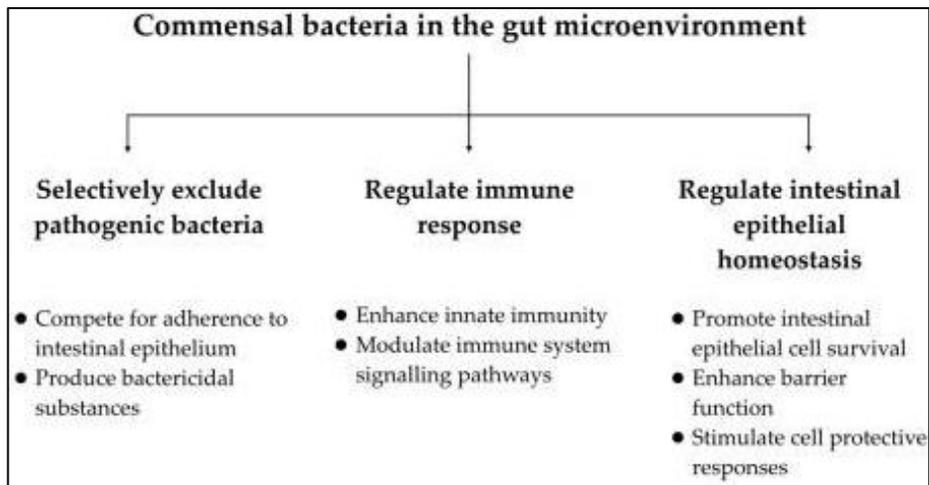


Figure 2. The benefits of probiotics in the treatment of colon cancer (35).

microbiota with probiotics has become useful for treating colon cancer (Figure 2). Probiotics offer a cheaper alternative to other cancer therapies and have fewer adverse side effects associated with them. Probiotics have the ability to decrease inflammation and combat pathogenic bacteria by producing bactericidal substances. The gut microbiome can regulate immune responses by enhancing innate immunity and modulating signaling pathways. They can also regulate intestinal epithelial homeostasis by promoting intestinal epithelial cell survival, enhancing barrier function, and stimulating cell protective responses (27). Probiotics can alter intestinal microflora enzyme activity, reduce carcinogenic secondary bile acids, bind carcinogens and mutagens, and increase short chain fatty acid production. Probiotics can also decrease DNA damage of the intestinal mucosa and help maintain intestinal barrier function (13).

Inflammatory effects on the gut microbiome and its role in Alzheimer’s disease

The microbiome plays an important role in the structural integrity and metabolic functions of the colonic mucosa through the production of SCFAs. Of the SCFAs, acetate, propionate, and butyrate are the most abundant in the gut lumen. Butyrate plays a role in maintaining intestinal health because it is the main energy source for the colonic mucosa and is fundamental in the regulation of gene expression, differentiation, inflammation, and apoptosis in host cells (33).

Studies in germ-free mice have shown that the lack of intestinal microbiota leads to an impaired immune function (36).

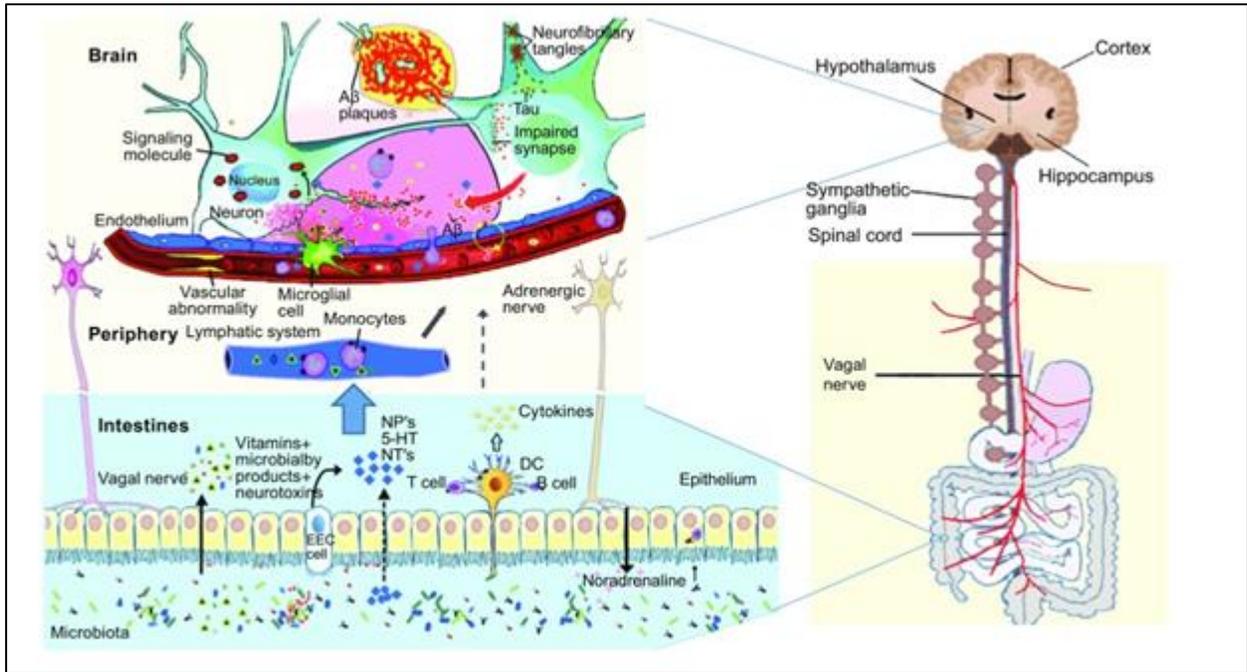


Figure 3. Pathogenesis of Alzheimer's disease and the role of the gut microbiome in neuroinflammation (48).

Inflammation was first implicated in the development and pathology of Alzheimer's disease in the 1990's with the finding of activated inflammatory cells and proteins surrounding the amyloid plaques and neurofibrillary tangles which are risk factors implicated in the development of AD (49). Brains that are affected by Alzheimer's disease are largely inflamed, and amyloid proteins respond to initial inflammation caused by the microbial infection attacking the brain (50).

Amyloid β plays a protective role in innate immunity, and it has been shown that inflammatory stimulus drives amyloidosis and amyloid β oligomerization. This function of amyloid β protects the brain from invading microbes. This is one hypothetical pathway of many that are tangled into the pathogenesis of Alzheimer's disease (Figure 3).

In dysbiotic conditions, there is increased permeability of the gut which is called the leaky gut. Microbes can traverse the leaky gut and enter the blood stream where they can then access the brain. The gut microbiome can influence the integrity of the blood-brain barrier. Disruption or absence of microbiota in mice has impaired the function of the blood-brain barrier and decreased cognitive function and memory formation (40).

Dysfunction of the gut epithelial barrier leads to peripheral inflammation. Therefore, the modulation of innate immune responses by changing microbial composition may exert healthy effects by slowing down or avoiding the progression of Alzheimer's disease (48). High fat diets and obesity are more common as of late and there is a link between cholesterol metabolism in the brain and amyloid β plaque formation in Alzheimer's disease (52). Thus, body fat and high blood sugar leads to a higher risk of AD development. A study performed comparing germ-free mice to conventional mice that were on a high-fat diet revealed that insulin sensitivity as well as cholesterol metabolism are metabolic targets that are influenced by the gut microbiome (53). In a different study done, the increase in risk of cardiovascular disease was tied to increased levels of circulating gut microbiota metabolites (54). The increased risk of cardiovascular disease (CVD) is important to Alzheimer's disease because CVD has recently become recognized as an etiologic hallmark for Alzheimer's disease (48). That is to say, CVD and vascular pathology play an important role in Alzheimer's disease.

The gut microbiome can control obesity which is the major cause of type 2 diabetes mellitus and is also linked to Alzheimer development. The gut microbiome controls obesity by influencing the activity of lipoprotein lipase (LPL) which is involved in releasing fatty acids from triglyceride-rich lipoproteins in the muscle, heart, and fat, and by affecting the expression of fasting-induced adipocyte factor protein (FIAF) (55). FIAF inhibits LPL activity and thus plays a role in preventing obesity. Microbes in the intestine can inhibit FIAF, which promotes adiposity by upregulating LPL in adipocytes and hepatic lipogenesis. When hepatic lipogenesis increases, more calories are consumed from the diet and converted into fat, which is stored in the liver. This process increases insulin resistance leading

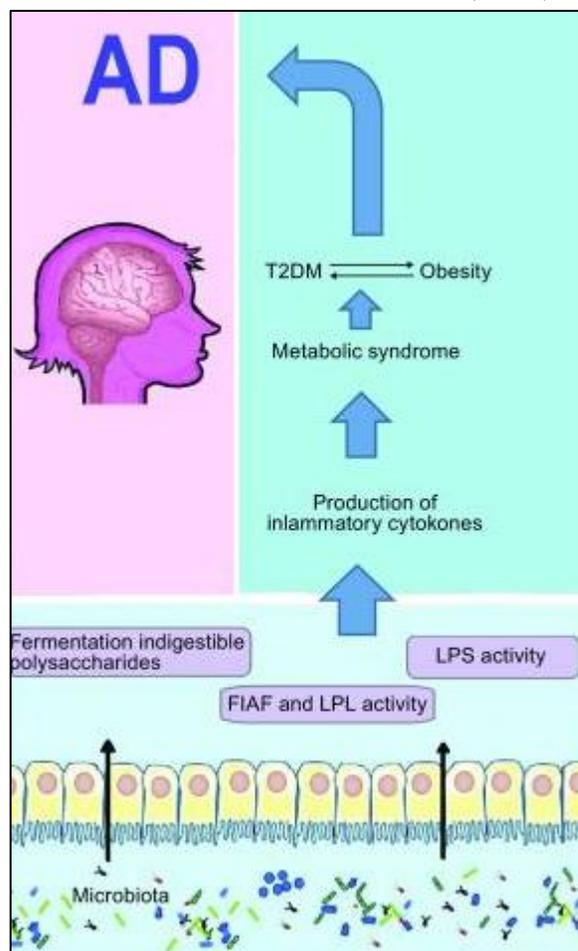


Figure 4. The link between the gut microbiome and obesity, and how this relates to AD (48).

to type 2 diabetes mellitus. As a result, there is an increased risk for obese individuals to develop Alzheimer's disease (Figure 4).

Recently proposed is the idea of a type 3 diabetes mellitus which is Alzheimer's disease. The reasoning behind this is that AD progresses as the brain develops resistance to insulin which prevents the uptake of lipids. Over time, these lipids will accumulate in the brain and cause stress and inflammation, along with dementia-related symptoms (45). It was observed in a study in which the path of insulin was blocked to rats' brains. When this pathway was blocked, the neurons deteriorated, and the rats became physically confused and their brains showed signs of AD (37). This animal model also brought about mechanisms connecting diabetes with Alzheimer's disease. One potential mechanism involves amyloid β clearance by insulin degradation enzymes. People with diabetes have an increased risk of developing Alzheimer's disease, and the link between these two diseases provides a new therapeutic approach for treatment of AD.

Probiotics and Alzheimer's disease

Since the gut microbiome plays a role in the progression of Alzheimer's disease, probiotics are an important therapeutic method for its treatment. These bacteria do not need to be alive, because the products of them (e.g. cell walls and bacterial DNA) have also proven to modulate the profile of the gut microbiome and immune response (48). The main beneficial effects provided by probiotics are to function as the first barrier to pathogenic organisms, produce substances that have antimicrobial effects, and to stimulate the immune processes of the host. Some strains of lactic acid bacteria produce vitamin B12 which is linked to AD because many studies show that vitamin B12 is lower in AD individuals than in healthy individuals (15). In a randomized, double-blind and controlled trial with 60 AD patients, there was improved cognitive function and metabolic status in patients after a 12-week period of consuming a mixture of probiotics (16). Probiotics have shown the ability to rebuild microbiota and restore health.

The role of the gut microbiome in Crohn's disease

Inflammatory bowel disease is composed of two different conditions. One being ulcerative colitis, and the other being Crohn's disease. IBD used to be considered a Western disease but it is becoming more common globally. Dysbiosis is likely to be the defining event in the

development of IBD. The most noted microbe change in patients with IBD is the reduced amount of the phyla *Firmicutes*. There have also been increases in bacteria from the phylum *Bacteroidetes*. Most pathogenic bacteria in humans are from the phylum *Proteobacteria*, which has been found to have a key role in IBD. An increase in this bacterial species indicates that it has an aggressor role in the initiation of chronic inflammation in patients diagnosed IBD. In addition, there have also been increases in *Escherichia coli* in ileal CD. This increase in pathogenic bacteria with the ability to adhere to the intestinal epithelium affects the permeability of the intestine, alters the diversity and composition of the gut microbiota, and induces inflammatory responses by regulating the expression of inflammatory genes, which consequently leads to the induction of intestinal inflammation (47).

The gut microbiome is a big cause of immune stimulation. The colonic epithelium lies close to a large number of diverse bacteria which leads to continuous communication between the cells of the host and those of the microbes. The continuous communication allows for the maintenance of homeostasis. In people with IBD, this balance gets disturbed which leads to host immune defects and inflammation of the GI tract.

Firmicutes and *Bacteroidetes* produce SCFAs from indigestible carbohydrates, and one of which, butyrate, is a primary energy source for colonic epithelial cells. Patients with IBD have decreased levels of SCFAs, which may be a key factor that comprises the intestinal and immune homeostasis. The decreased production of SCFAs affects the differentiation and expansion of T reg cells and the growth of epithelial cells, which are an important part of maintaining intestinal

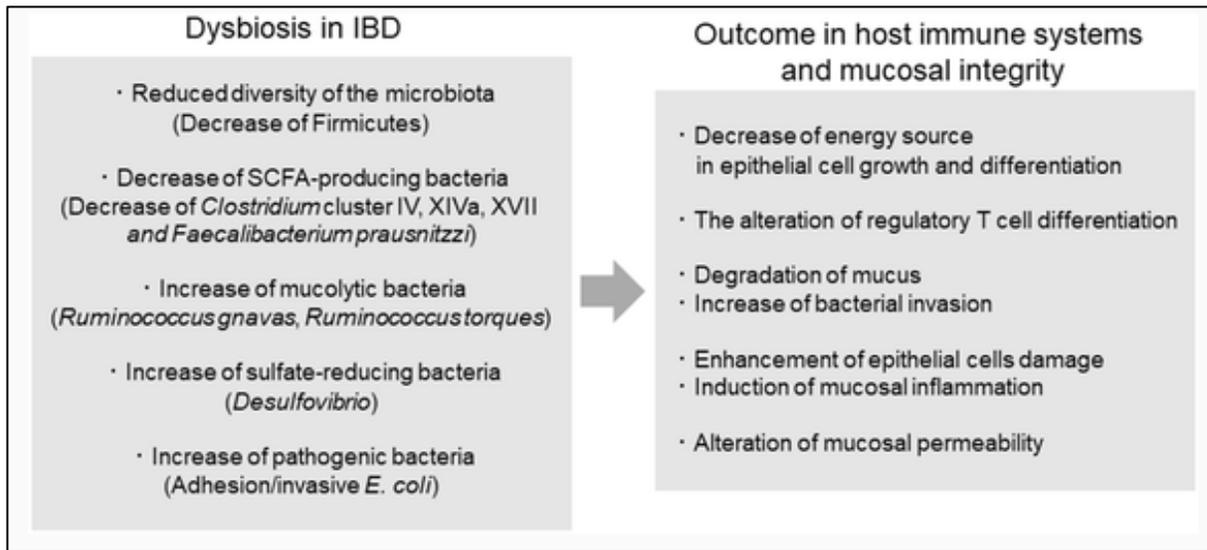


Figure 5. The outcomes of patients with dysbiosis in IBD (46).

homeostasis (51). Also, the number of sulfate-reducing bacteria is high in IBD patients, which results in the production of hydrogen-sulfate that damages intestinal epithelial cells and induces mucosal inflammation (19). Together, this information indicates that there is alteration of the gut microbiome associated with the pathogenesis of IBD.

There is a decrease in bacteria with anti-inflammatory capacities and an increase in bacteria with inflammatory capacities in patients with IBD as compared to healthy individuals (46). The outcome of dysbiosis and IBD is described in Figure 5.

Using probiotics for treatment of Crohn's disease

Probiotics can influence the gut microbiome composition, metabolic activity, and immunomodulation in a manner that is beneficial to the host (42). They can alter the microbial diversity through competitive inhibition of other bacteria, increase the mucosal barrier function by producing SCFAs, and interact with dendritic cells to stimulate an anti-inflammatory response. Some bacteria, such as *Lactobacillus*, *Bifidobacterium*, and *Streptococcus* have a clinical effect on GI inflammation (43).

There has been several studies showing the beneficial effects of probiotics in studies with patients with ulcerative colitis. In contrast, there has been limited evidence on the effectiveness of probiotics for the treatment of Crohn's disease. In one study, 45 patients with CD randomly received either 12 billion *Lactobacillus* or an identical placebo for one year (41). As a result, there was a clinical recurrence of 16.6% in the patients with *Lactobacillus*, and a recurrence of

10.5% in patients with the placebo. Another study involved 75 children in medically induced remission from Crohn's disease (2). The patients were randomly selected to receive 10 billion *Lactobacillus* or a placebo for 2 years as an adjunct to standard maintenance treatment. 31% of the children on *Lactobacillus* relapsed during the study period, and 17% of children on the placebo relapsed. A few explanations for the ineffectiveness of probiotics in this instance could be attributed to the fact that CD is a complex disease and the course of pathogenesis follows different phases, thus effectiveness may depend on the stage of Crohn's disease. Also, there are numerous species of probiotics, a different type may be more effective in the treatment than the commonly utilized *Lactobacillus*.

Additional applications

It has been recently evidenced that patients with Parkinson's disease (PD) also display an altered gut microbiome as was seen in patients with colon cancer, Alzheimer's disease, and Crohn's disease. A group of researchers showed that the gut microbiota is required for events that promote motor deficits in patients with PD (56). They did this by using germ-free mice that had bacteria depleted by antibiotics; the mice that overexpressed α Syn (involved in the pathogenesis of PD) had reduced microglia activation and motor deficits when compared to germ-free mice with a complex microbiota. The combination of overexpressed α Syn (related to genetics) with dysbiotic conditions influences the outcome of Parkinson's disease in mice. Treatment with SCFAs that are produced by gut microbes were found to restore the major features of disease in germ-free mice which identifies potential molecular mediators involved in gut-brain signaling (56). One potential pathway connecting α Syn to gut microbes is the microbe-dependent effects on microglia. The gut microbiota play an active role in promoting the maturation and inflammatory capabilities of microglia by producing SCFAs (57). SCFAs have the ability to cross the blood brain barrier and can thus affect cells in the central nervous system. Increased activation of microglia alters neuronal function and increases cell death in PD and other neurodegenerative disease (58). An inflammatory environment then causes aggregation of α Syn which further activates more microglia leading to a positive feedback loop and progression of the disease. If this potential mechanism is true that would indicate that future treatment options should include targeting immune activation by the microbiota (56).

Conclusion

Inflammatory bowel disease is caused by inflammation in the GI tract which increases the chance of colon cancer to develop and activates the NF- κ B pathway. This pathway mediates the production of pro-inflammatory cytokines which are involved in the pathogenesis of colon cancer. The NF- κ B pathway also regulates tumor necrosis factor. The two together work to promote cell proliferation and survival, causing tumor progression. Dysbiosis of the GI tract leads to inflammation and a leaky gut. Cytokines and growth factors are activated and work to enhance the growth and survival of dysplastic cells, contributing to malignant transformation in colon cancer. Another factor that contributes to inflammation of the GI tract is obesity, which exacerbates colon cancer. Increased consumption of fiber will decrease the risk of CRC, whereas consumption of red meat and animal fiber will increase the risk. High fat diets lead to inflammation and increased intestinal permeability, and high fiber diets lead to an increase in metabolites such as SCFAs which are the primary source of energy for colonic epithelia. Probiotics are used to treat colon cancer because they can restore the balance of the gut microbes and reduce inflammation. Among many beneficial functions, probiotics also work to reduce DNA damage and maintain the intestinal barrier.

Amyloid plaques are associated with the development of Alzheimer's disease, and patients diagnosed with the disease suffer from brain inflammation due to microbial infections. Microbes have access to the brain due to inflammation of the gut leading to increased intestinal permeability, and microbes travelling systemically in the blood. High fat diets have been linked to Alzheimer's disease due to cholesterol metabolism in the brain and amyloid plaque formation. Increased levels of body fat and high blood sugar puts a person at risk for developing Alzheimer's disease. There is a proposed idea of a type 3 diabetes which is related to the brain becoming resistant to the effects of insulin. This causes a build-up of lipids in the brain which creates inflammation and dementia-like symptoms to occur. Probiotics have been useful for the treatment of Alzheimer's disease because they provide a barrier to pathogenic bacteria, produce antimicrobial substances, and emulate the immune system of the host.

Dysbiosis is the leading cause for the development of IBD. The gut microbiome is imbalanced and there is an increase in pathogenic bacteria within the gut. The presence of pathogenic

bacteria in the gut causes inflammation to occur and permeability of the intestine to increase. There is also a decrease in the production of SCFAs in patients that have IBD, which leads to an impaired immune system and compromised intestinal homeostasis. Probiotics can be useful for IBD because they restore microbe homeostasis in the GI tract and increase the mucosal barrier function. Furthermore, probiotics they can reduce inflammation in the gut. Though they have proven their usefulness in cases of ulcerative colitis, their effectiveness has not been evidenced in cases of Crohn's disease, thus requiring more research to be performed.

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