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The Importance of the Human Microbiome in Developing and Maintaining a Healthy Neuroendocrine Immune System and Responding to Vaccines

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Abstract

The human microbiome interacts with the nervous, endocrine and immune systems that are extensively connected with each other. The status of the human microbiome in the skin, mouth, mucosal surfaces, anus, genitals, lungs and even human milk affects one's immune system and response to vaccines. The immune system is an integral part of the signaling pathways in the gut-brain axis. Bacteria in the gut can activate the vagus nerve, which has important functions in the neuroendocrine immune system. There is also a mucosal immune system, since the gastrointestinal epithelium is in close proximity to potentially pathogenic Bacteria, viruses, fungi and helminths. At the same time, the microbiome, hormones and the human host all work together to help maintain a healthy neuroendocrine immune system. This inter-kingdom form of communication has been called microbial endocrinology. The gut microbiome is part of the gastrointestinal (GI) tract, which contains the highest concentration of immune cells in the body. In a healthy gut, the microbiome balances the immune response. Commensal Bacteria inhibit immune responses within their niche, while directing them towards pathogens and uncontrolled growth. Short chain fatty acids (SCFAs) produced by Bacteria in the gut suppress inflammation and cancer. When the gut microbiome is healthy and functioning properly, there is a tight epithelial junction that forms a colonic, ileal, jejunal and gastric barrier. The intestinal lumen acts as a barrier against Bacteria and food antigens. However, gut microbiome dysbiosis can disrupt the structure and function of the barrier. This can cause pro-inflammatory lipopolysaccharides (LPS) to leak out of the gut and cause smoldering (low-grade) inflammation. Moreover, when the gut microbiome is unbalanced (dysbiosis), there is less biodiversity and an outgrowth of pathological Bacteria. This can cause inadequate immune function and inflammatory responses due to an imbalance between pro- and anti-inflammatory lymphocytes, GI motility and permeability. At the same time, the enteric virome is in a continuous and dynamic equilibrium with other components of the gut microbiome and the host's neuroendocrine immune system. Dysbiosis in the human gut that is caused by portions of the virome can trigger autoimmune diseases and cancer. Even though fungi are a small percentage of the human oral microbiome by number, their relatively large size (compared to Bacteria) means that they are a sizable portion of the biomass. This enables them to interact with Bacteria to form a stable biofilm that acts as an important structural component of the oral cavity. So, fungi and Bacteria work together synergistically to help their hosts develop a healthy and robust immune system.

Keywords: *Vaccines; Immune-Neuroendocrine System; Short Chain Fatty Acid (SFCAs); Enteric Nervous System (ENS); Gastric Barrier; Lipopolysaccharides (LPS)*

Abbreviations

2-AG: 2-Arachidonoylglycerol; 5-HT: 5-Hydroxy-L-Tryptophan; AEA: Anandamide; ANS: Autonomic Nervous System; ASD: Autism Spectrum Disorders; ASVD: Atherosclerotic Vascular Disease; CB1 and CB2: Cannabinoid Receptors 1 and 2; CNS: Central Nervous System; DHA: Docosahexaenoic Acid; DNA: Deoxyribonucleic Acid; ECs: Enterochromaffin Cells; EECs: Enteroendocrine Cells; ENS: Enteric Nervous System; EPA - (5Z,8Z,11Z,14Z,17Z): 5,8,11,14,17-Eicosapentaenoic Aid; FAAH; Fatty Acid Amide Hydrolase; GBA: Gut-Brain Axis; GIT: Gastrointestinal Tract; HGC: High Gene Count; HIV: Human Immunodeficiency Virus; HMP: Human Microbiome Project; HPA axis:

Hypothalamic-Pituitary-Adrenal Axis; IBD: Irritable Bowel Disease; IBS: Irritable Bowel Syndrome; IgG: Immunoglobulin; IL: Interleukin; LPS: Lipopolysaccharides; mM: mmols/L; mRNA: Messenger RNA; NF-κB: Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B cells; OUT: Operational Taxonomic Units; PAMPS: Pathogen-Associated Molecular Patterns; PANDAS: Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal Infections; PANS: Pediatric Acute-Onset Neuropsychiatric Syndrome; RA: Rheumatoid Arthritis; RNA: Ribonucleic Acid; SCFAs: Short Chain Fatty Acids; T1D: Type-1 Diabetes; TJ: Tight Junction; TLRs: Toll-Like Receptors; Tregs: Regulatory T-Cells

Introduction

A healthy immune system is essential in preventing infectious diseases. Our protective immunity and response to vaccines are affected by the status of the microbiomes in our skin, mouth, mucosal surfaces, anus, genitals, lungs and even human milk [1-14]. Much of this protection comes from the fact that our microbiomes have evolved with our ancestors and established ecosystems that exclude pathogenic microorganisms but encourage the growth of healthy, commensal microorganisms. Once a baby is born, breastfeeding can help the baby develop a healthy microbiome, since mother's milk contains Bacteria (including *Staphylococcus* and *Streptococcus* species) and many important biochemicals, such as human oligosaccharides, that stimulate the growth of beneficial microbial communities, such as *Bifidobacterium* species [15]. On the other hand, exposure to antibiotics and/or acetaminophen can increase an infant's susceptibility to allergies [16].

Vaccines and the microbiome

Our response to vaccines is improved by a healthy microbiome, which acts as our natural adjuvant to optimize our immune response [1]. Moreover, a healthy microbiome helps to ensure that our immune system is properly regulated at both a steady state and when challenged by infections and/or cancer. It helps to control almost all aspects of our immune system, from hematopoiesis to the function of lymphocytes. Commensal Bacteria lower the threshold required to respond to infection, which enables a rapid and efficient response to pathogenic infectious microbes. A healthy microbiome helps to control the development of the immune system, the level of innate immune responses and the induction of effector and regulatory responses. It exerts its control by producing metabolites, such as butyric acid (or butyrate at a physiological pH), by activating inflammasomes and by acting on epithelial cells. It ferments polysaccharides in dietary fiber and other parts of plants to produce short chain fatty acids (SCFAs), including butyrate. These SCFAs promote the differentiation of B cells into plasma cells. A healthy microbiome also exerts systemic control of the immune system since it constitutively activates the response of our antibodies to the gut microbiome, thus preventing it from spreading throughout the body. Moreover, some of the antibodies against our commensal Bacteria can cross-react with pathogenic viruses, such as HIV. The pre-existing immune response to our microbiome helps to control our response to vaccines – especially those that use 'live' attenuated viruses or organisms. Our microbiome also increases our response to the seasonal trivalent influenza vaccine and the polio vaccine. On the other hand, a dysfunctional gut microbiome can lead to vaccine failure. For example, oral vaccines for Rotavirus, Poliomyelitis, *Vibrio cholerae* and *Shigella* that are given to children in countries that have a relatively low average income fail to protect as m as when given to higher-income countries. In addition, malnutrition and chronic exposure to pathogens can lead to a 'leaky gut' with systemic leakage of microbes and subsequent inflammation. This increased inflammatory tone can adversely affect one's immune response to vaccines and prevent the establishment of a healthy memory pool [1].

In addition, "systems vaccinology has emerged as a multidisciplinary field that combines modern high-throughput technologies, computational modeling and conventional immunology to provide a holistic view of the molecular mechanisms of vaccine-induced immunity" [4]. The goal is to determine all of the interactions and metabolic pathways that link commensal microbes with their human host. This is leading to new vaccines for yellow fever, influenza, meningococcal infections and malaria. In the process, early biomarkers in the immune system can be used to predict the responses of CD8+ T cells and antibodies to vaccines [4].

The nasal microbiome affects a person's response to the live attenuated influenza vaccine that is administered intra-nasally [2]. This vaccine changes the nasal microbiome to allow operational taxonomic units (OTUs) that are less abundant to establish a new community

niche. So, the abundance of several bacterial species is linked to this vaccine. Two of them (*Prevotella melaninogenica* and *Veillonella dispar*) were already known to be related to respiratory health. Hopefully, systems vaccinology will lead to new and better, as well as more personalized and effective vaccines [2].

The neuroendocrine immune system

However, the human immune system does not work in isolation. It is extensively connected with the nervous system and endocrine system. So, this has been called the immune-neuroendocrine system and neuroendocrine immune system [17-19]. The human microbiome is an essential part of this system [20]. There is an extensive communication network among different microbes and between microbes and human eukaryotic cells. Commensal and pathogenic Bacteria interact with the central, autonomic and enteric nervous systems (CNS, ANS and ENS, respectively), as well as the hypothalamic-pituitary-adrenal (HPA) axis [21]. These interactions form the gut-brain axis (GBA). The interactions go both ways in a bidirectional network of communication. This network connects the emotional and cognitive centers of the brain with peripheral intestinal functions through neural, endocrine, immune, and humoral links. These interactions contribute to both health and disease [22]. Biochemicals that are produced within the gut lumen influence the intrinsic enteric neurons in the ENS both directly and indirectly. For direct actions to occur, a biochemical must pass through the epithelial barrier to access the nerve endings on enteric sensory neurons. They are in the connective and muscular tissue immediately beneath the intestinal epithelium. In a healthy gut with an intact epithelial barrier, bacterial products can only get through the barrier by active or inactive transport or by transcytosis. In an unhealthy gut in which the epithelial barrier is damaged by inflammation ('leaky gut'), both Bacteria and their products can pass between cells whose tight junctions are no longer intact [22].

There are also indirect interactions between the Bacteria in the lumen and the ENS [22]. This occurs through endocrine or immune cells in the gut. Enteroendocrine cells in the epithelium can release paracrine signals that are detected by sensory neurons that innervate the gut. One set of enteroendocrine cells called enterochromaffin cells (ECs) can transduce signals that convert bacterial stimuli into downstream neuronal responses. Enteric neurons also express toll-like receptors (TLRs) that detect bacterial pathogen-associated molecular patterns (PAMPs). Lipopolysaccharides (LPS) that are produced by gram-negative Bacteria are an important example. They are detected by TLR4. Enteric neurons activated by TLR-4 regulate neuronal survival and gut motility. In addition, TLR2 can detect peptidoglycans and lipoproteins from gram-positive Bacteria. TLR2 signaling affects the structure of the ENS, as well as intestinal contractility [22].

Bacteria in the gut can activate the vagus nerve [23]. It is the tenth cranial nerve. It innervates the pharynx, larynx and visceral organs. It is the main afferent pathway from the gut to the brain. Also, information from the heart, lungs, pancreas, liver, stomach and intestines are delivered tonically to the brain through sensory fibers in the vagus nerve. There are an estimated 30 000 to 80 000 vagal afferent nerves that supply the intestines with a 9:1 ratio of afferent to efferent fibers. The endings of visceral afferent endings have receptors for several different hormones and regulatory peptides, such as ghrelin, glucagon-like peptide-1, cholecystokinin and peptide YY. They affect food intake, satiety and energy balance. Butyrate affects vagal afferent nerve terminals. In addition, the vagus nerve can affect health and behavior. This includes lethargy, depression, anxiety, loss of appetite and sleepiness – especially when the vagus nerve is stimulated by pro-inflammatory LPS or interleukin-1β. In contrast, other types of stimulation of the vagus nerve can cause a reduction in anxiety and depression, which helps the neuroendocrine immune system. For example, dietary omega-3 polyunsaturated fats, such as docosahexaenoic acid (DHA) and (5Z,8Z,11Z,14Z,17Z)-5,8,11,14,17-eicosapentaenoic acid (EPA) increase vagal tone [23]. Note that DHA is also an abbreviation for dehydroascorbic acid, the oxidized form of ascorbic acid, or vitamin C. Of course, the abbreviation EPA usually stands for the U.S. Environmental Protection Agency. The structures of docosahexaenoic acid and dehydroascorbic acid are compared in figure 1. The structure of EPA is shown in figure 2.

Moreover, vagal stimulation is used to treat refractive epilepsy and intractable depression [23]. The vagus nerve also has important functions in the immune system. It senses pro-inflammatory afferent signals sent to the afferent regions of the brain and activates anti-inflammatory efferent responses. Moreover, the gut microbiome affects the ENS, as well as the brain and behavior. It has also been sug-

gested that improper regulation of inflammation that occurs in major depressive disorder may be caused (at least in part) by gut microbiome dysbiosis, or imbalance in the microbial ecosystem. This is an extension of the hygiene hypothesis. It states that the large increases in autoimmune diseases and allergies that are occurring are due in part to the large-scale eradication of Bacteria in clean, modern, indoor environments [23].

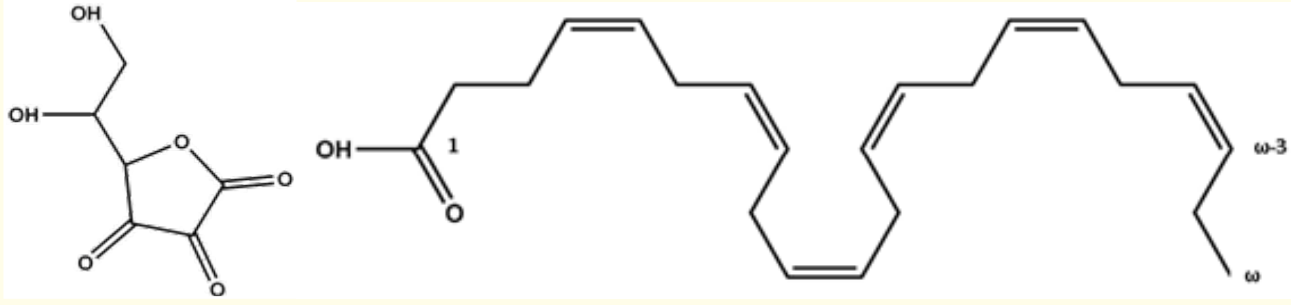

Figure 1: *2D structure of dehydroascorbic acid (left) and docosahexaenoic acid (right), which are both abbreviated as DHA.*

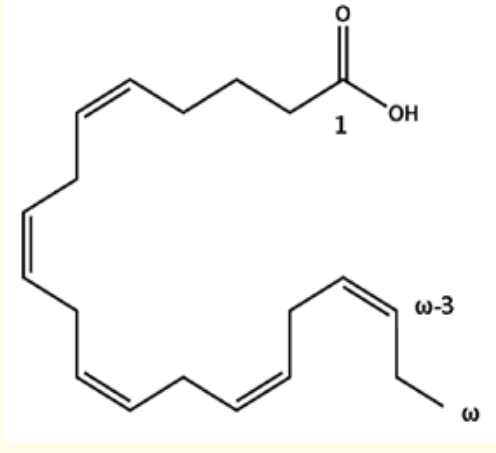

Figure 2: *2D structure of (5Z,8Z,11Z,14Z,17Z)-5,8,11,14,17-eicosapentaenoic aid (EPA), an omega-3 polyunsaturated fatty acid.*

Another way that the ENS, gut microbiome and the rest of the body communicate is through the endocannabinoid system [24]. It is widely distributed throughout the brain and most of the rest of the human body. There are two cannabinoid receptors, CB_1 and CB_2. The CB_1 receptor exists in the ENS, while the CB_2 receptor is found mostly in the immune system. Their endogenous ligands are anandamide (AEA) and 2-arachidonoylglycerol (2-AG). Their structures are shown in figures 3 and 4. Anandamide is also known as N-arachidonoylethanolamine.

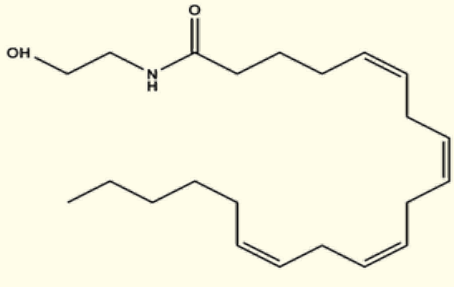

Figure 3: *2D structure of anandamide (AEA), the endogenous ligand for the CB1 cannabinoid receptor.*

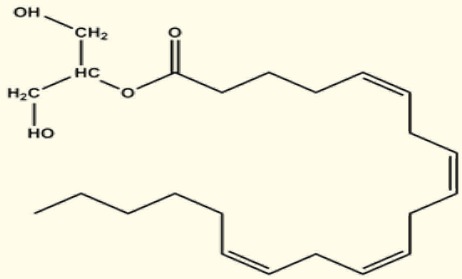

Figure 4: *2D structure of 2-arachidonoylglycerol (2-AG), the endogenous ligand for the CB2 cannabinoid receptor.*

Activated CB_1 receptors in the ENS inhibit motility in the gastrointestinal tract (GIT) [24]. Like CB_2, it is a G protein-coupled receptor (GPCR). Both are coupled to $G_{i/o}$ proteins that inhibit adenylate cyclase, trigger the mitogen activated protein kinase (MAPK) signaling system, inhibit N- and P/Q-type Ca^{2+} channels and activate A-type outward K^+ channels. These activities prevent the influx of Ca^{2+} into the cell, block membrane depolarization and inhibit the release of acetyl choline, the fast excitatory neurotransmitter in the ENS. In addition, the gut microbiome can affect the endocannabinoid tone [24], which is measured by the amount of mRNA coding for the CB_1 receptor and the fatty acid amide hydrolase (FAAH), as well as the concentration of AEA [25]. The FAAH is the main enzyme that catalyzes the hydrolysis of AEA [25]. That is, EAE and 2-AG can be stored as ligands that are tightly bound to fatty acid binding proteins [26]. They can diffuse in the lipid bilayer to bind to CB receptors. So, they can act as autocrine or paracrine stimulators of CB_1 and CB_2, thus giving the appearance of constitutive activity [26].

Whether activated by EAE that is stored on fatty acid binding proteins or released at synapses, the endocannabinoid system links the gut microbiome to adipogenesis, obesity and diabetes, which damage the immune system [15,27]. Obesity can lead to an increased tone in the part of the endocannabinoid system that is located in adipose tissue. Adipocytes produce adipokines like apelin that affect glucose homeostasis, the CNS and the cardiovascular system. Gut Bacteria can produce LPS that are pro-inflammatory and stimulate the synthesis of endocannabinoids. However, during normal, healthy conditions, endocannabinoids down-regulate the expression of apelin and its receptor [27]. On the other hand, endocannabinoid deficiency can lead to anxiety as well as intestinal disorders, such as irritable bowel syndrome (IBS) [25].

Connections between the gut microbiome, ENS, brain and immune system

The gut and brain communicate with each other through anatomic and humoral pathways. Intervening with one system will affect the other [28]. There is an intestinal epithelial layer that forms a very selective barrier that helps maintain homeostasis by coordinating the actions of the different types of cells within the layer. It is important for maintaining good health. There are enteroendocrine cells (EECs) at the base of intestinal crypts. They transduce mechanical and chemical signals from the intestinal lumen to neighbor cells and the local neuronal network. One of the types of EECs, the enterochromaffin (EC) cells, are the main source of 5-hydroxytryptamine (5-HT, also known as serotonin) in the human body. Serotonin that is released from EC cells mediates many functions of the GIT, including secretion, peristalsis, vasodilation, perception of pain and nausea. It is biosynthesized from the essential amino acid, L-tryptophan. First, tryptophan is converted to 5-hydroxy-L-tryptophan, which is converted to 5-HT in a reaction catalyzed by 5-hydroxytryptophan decarboxylase and its coenzyme pyridoxal phosphate (the active form of vitamin B_6). However, L-tryptophan can also be metabolized to kynurenic acid, which an antiexitotoxic and anticonvulsant compound. During stressful conditions that harm the immune system, the 5-HT biosynthetic pathway competes with the kynurenic acid pathway for L-tryptophan. This decreases the plasma concentration of 5-HT. So, changes in the 5-HT metabolism may help cause IBS and other disorders of the GIT. Also, IBS patients have lower mucosal and higher plasma concentrations of both kynurenic acid and 5-HT, compared to healthy patients. There is also a positive correlation between signs of depression and the 5-HT concentration in mucosa but not in blood plasma [28].

There is also a mucosal immune system, since the gastrointestinal epithelium is in close proximity to potentially pathogenic Bacteria, viruses, fungi and helminths [28]. This local immune network contains macrophages, lymphocytes and dendritic cells. It is required for the maintenance of homeostasis between the human host and luminal microbiome. Stress hormones that are organized in the HPA axis are part of the humoral communication between the intestinal tract and the CNS. The ENS is highly innervated by intrinsic neurons that are found in groups in the myenteric and submucous plexus. Then there is the vagus nerve, which has essential roles in communication between the gut and the brain. It is one of the twelve nerves that innervate the thoracic and abdominal tissues. There is a left and right cervical pathway. They have afferent and efferent projections that converge in the cranium where either information coming from other organs is processed or chemical signals are sent to peripheral tissues [28]. So, the gut microbiome and the ENS affect the neuroendocrine immune system and autoimmune diseases.

For example, microbial metabolism in the gut plays an important role in irritable bowel disease (IBD) [29]. The gut microbiomes of infants can also affect their susceptibility to type-1 diabetes (T1D) and distinguish between infants who will be most likely to progress into T1D and those who will not [30]. The gut microbiome is also an important part of the ANS that is called the enteric nervous system, or ENS [31]. It influences anxiety and depressive-like behaviors as well as dysbiosis in autism spectrum disorder (ASD). Dysbiosis also happens in functional gastrointestinal disorders that can cause mood disorders and are linked to a disruption of GBA. Disruptions in the GBA can cause changes in intestinal motility and secretion. They also cause visceral hypersensitivity and lead to deleterious changes in the entero-endocrine and neuroendocrine immune system [31].

Enteric glial cells are also important in the ENS [32]. They form an extensive network in the mucosa of the GIT. Like glial cells in the central nervous system (CNS), enteric glia were originally thought to have merely supportive roles, but are now known to be actively involved in the ENS. They link enteric nerves, enteroendocrine cells, immune cells, and epithelial cells. Enteric glial cells also link the nervous and immune systems.

The development of the immune system also depends on a healthy gut microbiome [33]. Serotonin can modulate immune responses and influence intestinal inflammation. The immature immune system of babies and infants has a bias towards the T_H2 version of helper T-cells. The immune system shift towards a T_H1 bias as the gut is colonized with more Bacteria. Bacteria like *Bifidobacterium* and *Lactobacillus* promote this shift. However, administering broad-spectrum antibiotics can reduce the biodiversity of the gut microbiome and delay its colonization by some strains of *Bifidobacterium* and *Lactobacillus*. Moreover, the decreased diversity and stability of the gut microbiome can cause serotonin-related health problems in the elderly [33].

In a healthy gut, the microbiome balances the immune response. Commensal Bacteria inhibit immune responses within their niche, while directing them towards pathogens and uncontrolled growth. This balance is mediated by secreting metabolites and by intercellular signaling through activated toll-like receptors (TLRs) [34]. TLRs deactivate the local immune response [34,35]. SCFAs (acetic, propionic and butyric acids) suppress inflammation and cancer [35]. In contrast, undesirable Bacteria can produce an excess of secondary bile acids that can increase the concentration of reactive oxygen species (ROS), which cause smoldering inflammation as well as damage to DNA, proteins and lipids. Obesity is a known cause of gut microbiome dysbiosis. The secondary bile acid metabolite, deoxycholic acid (DCA), is produced by Bacteria in the phylum Firmicutes. They tend to be present at higher levels in the guts of obese people. A diet rich in red meat tends to increase the levels of *Fusobacterium nucleatum*, which causes DNA damage and genomic instability within developing tumors [34]. Also, *F. nucleatum* stimulates inflammation and can protect tumors from proper immunosurveillance and destruction. This increases the risk of colorectal cancer [36].

The benefits of vegan and vegetarian diets

In contrast, vegan and vegetarian diets can decrease the risk of not just cardiovascular diseases, but also autoimmune diseases and many types of cancer, as well as metabolic syndrome and diseases linked to it, including neurodegenerative diseases [37,38]. In a study

sponsored by Seventh Day Adventists, who preach the values of a vegetarian diet (the Adventist Study-2), vegetarian diets were found to be healthier than those of omnivores [39-41]. Four types of vegetarian diets were tested: vegan, lacto-ovo vegetarian, pescovegetarian, and semi-vegetarian [38,39]. Vegan diets had a unique advantage in that they lowered the incidence of type-2 diabetes [39,40] and decreased overall mortality [41].

There is another diet called the extreme raw vegan diet (encouraged by the Living Food movement) [37,42]. Patients with rheumatoid arthritis (RA) were placed on this diet for one month. The composition of their gut microbiomes changed significantly, while the symptoms of RA improved [42]. So, changing to a vegetarian and/or vegan diet can have very healthy effects that are mediated, at least in part, by the gut microbiome.

The healthy gut microbiome is your personal oncologist

While an unhealthy gut microbiome can cause diseases, including cancer, a healthy gut microbiome can act as your personal oncologist and help prevent cancer [43,44]. Bacteria in the gut produce SCFAs and other metabolites that help prevent cancer. The most abundant SCFAs are acetic, propionic and butyric acids, which exist as the anions acetate, propionate and butyrate at the physiological pH of about 7.3. Their combined concentration in the colon is about 50 - 150 mM (mmols/L) [43,44]. They account for about 90% of all the SCFAs and are present in a mole ratio of about 13:4:3 [45]. Butyrate is especially important. It is the main source of energy for colonocytes [46]. It regulates colonocyte differentiation and apoptosis by promoting removal of dysfunctional cells. This helps protect against colorectal cancer [47]. Butyrate is also essential for maintaining mucosal integrity, while modulating intestinal inflammation and promoting genome stability [43,44]. Non-digestible carbohydrates are fermented by Bacteria in the gut (primarily Firmicutes and Actinobacteria) to produce the SCFAs. Butyrate and propionate are especially important in preventing cancer, since they inhibit histone deacetylases in colon and immune cells. This downregulates the production of pro-inflammatory cytokines, such as interleukin-6 (IL-6) and IL-12 in colonic macrophages. Butyrate and propionate also induce the differentiation of important immune cells that help to control inflammation. In addition, some gut Bacteria contain enzymes that catalyze the biotransformation of dietary phenolic compounds that act as antioxidants [43,44].

Indirect effects of the gut microbiome

The composition of the gut microbiome can also affect one's health and neuroendocrine immune system indirectly by influencing one's state of mind, including happiness, sadness and depression [48]. That is, stress and anxiety can change the function of the gut and its microbiome. Several Bacteria in the gut can influence neural development, complex behaviors and nociception. So, the concept of "state of the gut" has been proposed to take the place of, or augment the concept of state of mind. So, changing the gut microbiome through therapeutic intervention may eventually be used to treat gastrointestinal and affective disorders [48].

When the gut microbiome is healthy and functioning properly, there is a tight epithelial junction that forms a colonic, ileal, jejunal and gastric barrier [48,49]. The intestinal lumen acts as a barrier against Bacteria and food antigens. However, gut microbiome dysbiosis can disrupt the structure and function of the barrier. This can cause pro-inflammatory biochemicals like lipopolysaccharides (LPS) to leak out of the gut and cause smoldering (low-grade) inflammation. The LPS can enter circulation through intracellular transport after binding to TLR4 that can be accesses through the impaired integrity of the tight junction (TJ). This can lead to metabolic diseases and endotoxemia. High-fat diets can also change the TJ, which increases the permeability of the TJ to LPS. Obesity can cause the ratio of gram-negative Bacteroidetes to gram-positive Firmicutes to decrease. In healthy, non-obese people, there is still a low concentration of LPS circulating in the blood. This is needed to help modulate the immune system. However, when the LPS concentration becomes too high, the excess LPS can form a complex with proteins that bind it and the CD14 co-receptor that is recognized by TLR4. In addition, saturated fatty acids can bind to TLR4. Activated TLR4 triggers intracellular signaling through the protein complex called NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells). It is a transcription factor that plays an essential role in the inflammatory response to infection. It is also the master regulator of pro-inflammatory cytokines and chemokines. However, dysegulation of NF-κB can lead to improper development of the neuroendocrine immune system, as well as the emergence of autoimmune diseases, septic shock, inflammatory diseases and cancer.

At the same time, a dysfunctional gut microbiome can produce other pro-inflammatory toxins, such as indoxyl sulfate, *p*-cresol sulfate, trimethylamine-*N*-oxide that can cause chronic kidney disease [49].

The immune system is so closely linked to the neuroendocrine system that it has been called the immune-neuroendocrine system [33]. So, when authors describe the effects imbalances in the gut microbiome and immune-neuroendocrine system on ASD, they are really describing an imbalance in the gut-immune-neuroendocrine system [50]. This imbalance in the GIT is evident through the higher incidence of acid reflux, constipation and diarrhea in patients who have ASD [51]. In addition, if the mother has an autoimmune disease, some of her IgG antibodies can be transferred to her fetus, making it more susceptible to ASD. Antibiotic treatment to the mother or neonate in the perinatal period, as well as sepsis or infection by pathogenic Bacteria can also increase the baby's susceptibility to ASD [51].

As mentioned previously, an imbalance in the gut microbiome can disrupt the structure and function of the tight epithelial junction that forms a colonic, ileal, jejunal and gastric barrier [49,52]. There are also reports that there is increased permeability or leaky intestines, as well as an imbalance in the neuroendocrine immune systems in many patients who have ASD [50]. This includes the peripheral blood and CNS. There is also a decrease in the levels of $CD4^+$ and $CD8^+$ lymphocytes, as well as albumin, gamma globulin and immunoglobulins (IgG, IgG2 and IgG4). Also, the function of the blood-brain barrier is impaired in ASD [50].

Cross-talk between the gut microbiome and the immune system can inappropriately over-activate the neuroendocrine immune system when one is suffering from an imbalance [53]. When there are too many potentially pathogenic Bacteria in the gut, bacterial toxins like LPS and metabolites such as propionic acid can cause systemic and cellular damage. This can lead to systemic, smoldering inflammation and damage to neurons. When cells from both the innate and adaptive immune system are over-activated, the concentrations of tumor necrosis factor-α (TNF-α) and IL-1 can increase. This, in turn, can lead to inflammatory responses and over-activation of glial cells in the brain. This is consistent with the observation that microglia (the immune cells of the brain) are important mediators of neuroinflammation in ASD [53].

However, there is much more to learn. For example, even though exposure to antibiotics may increase a child's susceptibility to ASD, there is at least one case in which antibiotics seemed to cure ASD [54]. In contrast to other studies that seemed to show that the risk of ASD can increase after exposure to antibiotics, other studies showed an improvement in ASD symptoms [54,55]. Moreover, antibiotics are given routinely to treat symptoms of ASD that are associated with Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal infections (PANDAS), Pediatric Acute-onset Neuropsychiatric Syndrome (PANS), and chronic Lyme disease [53,56,57]. Those antibiotics target pathogenic Bacteria, such as *Streptococcus* and *Borrelia* [53]. However, antibiotics are not usually given to treat other groups of ASD patients if the only goal is to relieve its symptoms and not to clear up a potentially dangerous bacterial infection [53]. Still, vancomycin was used in one clinical trial to manage symptoms of ASD, since it does target just a few strains of Bacteria [53,58].

The importance of a healthy oral microbiome

One of the worst examples of how reductionist thinking can contribute to misunderstanding and serious health problems is the way that dental health is frequently ignored. Most physicians simply know that the teeth are located in the one of the filthiest parts of the body (the mouth) and are someone else's business (dentists). Moreover, many health insurance plans (including Medicare) don't cover dental procedures or even routine preventative dental care. The idea is that you can still eat even if you don't have teeth. However, such thinking has led to an epidemic of periodontal disease and malnutrition – especially in the elderly. If this only meant that many people suffer some pain that can be treated with a local anesthetic, it would not be so bad. But it also means that many people are exposed to chronic bacterial infections and the attendant smoldering inflammation that can lead to Crohn's disease, diabetes, atherosclerosis, cardiovascular diseases, many types of cancer and neurodegenerative diseases [59-64].

Periodontal disease was once thought to be due primarily to a triad of oral anaerobic bacteria, *Porphyromonas gingivalis, Treponema denticola* and *Tannerella forsythia* [60]. However, metagenomics and mechanistic analyses have produced a new systems-based model

for the pathogenesis of periodontal disease. It states that there are other important Bacteria that interact with the classical triad. In this model, periodontal disease is not caused by just a few pathogenic Bacteria. It is caused by a synergistic interaction between many Bacteria that lead to an imbalance or dysbiosis. This changes the ecologically balanced biofilm that is associated with the healthy homeostasis that exists in periodontal tissue [60].

As a result, Bacteria that infect the mouths of people with periodontal disease can enter the bloodstream and circulate throughout the body. They can enter the heart and other parts of the body and cause diseases. As a result, there is a clear interaction between atherosclerotic vascular disease (ASVD) and periodontal disease [59]. Periodontal disease is an all too common chronic inflammatory condition that damages the structures that support the teeth. It affects the epithelial, connective and osseous (bone) tissues that surround the teeth. Bacteria that were attached to the teeth along the gingival margin before the onset of periodontal disease can grow and form biofilms that protect them, but harm the patient. At the same time, these Bacteria can induce an unfavorable immune response in adjacent gingival tissues. If the biofilm and inflammation migrate along the surface of the root, they can affect the structure that supports the tooth and become periodontitis [59].

Communication between the gut microbiome and immune-neuroendocrine system

The gut microbiome plays an important role in communications between the immune and neuroendocrine systems [33]. It can stimulate some of the immune cells in the gut. Subsequent cross-talk between the immune cells and enteric neurons has a major impact on human health and disease. The mature neuroendocrine immune system is continuously being stimulated by bacterial cells. It responds by producing lymphocytes and cytokines. As a result, the microbiome produces a chronic state of low-grade activation of the innate immune system. Cytokines that are released create a basal state of immune activation. The adult human gut can contain as much as 1g of LPS. As immune cells are exposed to LPS, mucosal homeostasis is established and maintained. In addition, *Bacterioides fragilis* produces a glycosphingolipid that inhibits the proliferation of natural killer T-cells in the colonic lamina propria and a polysaccharide that induces colonic regulatory T-cells (Tregs). At the same time, the motility of the GIT is regulated by interactions between the ENS, microbiome and macrophages that are near the myenteric plexus and intestinal cells of Cajal. However, when the gut microbiome is unbalanced (dysbiosis), there is less biodiversity and an outgrowth of pathobionts. This can cause inadequate immune function and inflammatory responses due to an imbalance between pro- and anti-inflammatory lymphocytes, GI motility and permeability. This can lead to further changes outside the intestines, including the neuroendocrine immune system. For example, increased production of cytokines is linked to systemic inflammation and high concentrations of pro- and anti-inflammatory cytokines, as well as cortisol and norepinephrine concentrations in the saliva and blood plasma. Increased concentrations of cytokines and neuropeptides have been linked to disrupted sleep, depression, increased anxiety, impaired long-term memory for emotional stimuli and increased sensitivity to visceral pain. The gut microbiomes of elderly patients in particular can produce more LPS, which can lead to endotoxemia [33].

Conclusion

In conclusion, a healthy neuroendocrine immune system is essential in preventing infectious diseases. Our protective immunity and response to vaccines is affected by the status of the microbiomes in our skin, mouth, mucosal surfaces, anus, genitals, lungs and even human milk. Our response to vaccines is improved by a healthy microbiome, which acts as our natural adjuvant to optimize our immune response [1]. Moreover, a healthy microbiome helps to ensure that our immune system is properly regulated at both a steady state and when challenged by infections and/or cancer. It helps to control almost all aspects of our immune system, from hematopoiesis to the function of lymphocytes. The pre-existing immune response to our microbiome helps to control our response to vaccines – especially those that use 'live' attenuated viruses or organisms. Our microbiome also increases our response to the seasonal trivalent influenza vaccine and the polio vaccine. On the other hand, a dysfunctional gut microbiome can lead to vaccine failure. However, the human immune system does not work in isolation. It is extensively connected with the nervous system and endocrine system. So, this has been called the immune-neuroendocrine system and neuroendocrine immune system. The human microbiome is an essential part of this system. There

is an extensive communication network among different microbes and between microbes and human eukaryotic cells. There is also a mucosal immune system, since the gastrointestinal epithelium is in close proximity to potentially pathogenic Bacteria, viruses, fungi and helminths. This local immune network contains macrophages, lymphocytes and dendritic cells. It is required for the maintenance of homeostasis between the human host and luminal microbiome. Stress hormones that are organized in the HPA axis are part of the humoral communication between the intestinal tract and the CNS. The ENS is highly innervated by intrinsic neurons that are found in groups in the myenteric and submucous plexus. Then there is the vagus nerve, which has essential roles in communication between the gut and the brain. It is one of the twelve nerves that innervate the thoracic and abdominal tissues. Bacteria can produce an excess of secondary bile acids that can increase the concentration of ROS, which cause smoldering inflammation and damage to DNA, proteins and lipids. Obesity is a known cause of gut microbiome dysbiosis. The secondary bile acid metabolite, deoxycholic acid (DCA), is produced by Bacteria in the phylum Firmicutes. They tend to be present at higher levels in the guts of obese people. A diet rich in red meat tends to increase the levels of *Fusobacterium nucleatum*, which causes DNA damage and genomic instability within developing tumors [34]. Also, *F. nucleatum* stimulates inflammation and can protect tumors from proper immunosurveillance and destruction. This increases the risk of colorectal cancer. In contrast, vegan and vegetarian diets can decrease the risk of not just cardiovascular diseases, but also autoimmune diseases and many types of cancer, as well as metabolic syndrome and diseases linked to it, including neurodegenerative diseases. The composition of the gut microbiome can also affect one's health and neuroendocrine immune system indirectly by influencing one's state of mind, including happiness, sadness and depression. That is, stress and anxiety can change the function of the gut and its microbiome. A healthy oral microbiome is also important for good health. In contrast, periodontal disease with the attendant chronic bacterial infections and smoldering inflammation can lead to Crohn's disease, diabetes, atherosclerosis, cardiovascular diseases and many types of cancer as well as neurodegenerative diseases. The gut microbiome plays an important role in communications between the immune and neuroendocrine systems [33]. It can stimulate some of the immune cells in the gut. Subsequent cross-talk between the immune cells and enteric neurons has a major impact on human health and disease. The mature neuroendocrine immune system is continuously being stimulated by bacterial cells. It responds by producing lymphocytes and cytokines. As a result, the microbiome produces a chronic state of low-grade activation of the innate immune system. So, a healthy microbiome is important for many aspects of human health.

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Conflict of Interest

The author declares that there is no conflict of interest.

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