HIGH SCHOOL EDITION
Journal of Student Research
Volume 11 Issue 4 (2022)

The Gut Microbiome: An Overview

Shelly Dimri[1] and Angela Rizzo[#]

[1] George C. Marshall High School, USA
[#]Advisor

ABSTRACT

As a rapidly growing field of research over the past two decades, the Gut Microbiome has emerged as an important player with an integral role in human body functions. Its perturbed function correlates with several diseases such as diabetes, obesity, liver dysfunction, degenerative conditions, and neurological conditions. Studies utilizing the technological advancements with multi-omics methodologies continue to allow the detection and identification of gut microbes and provide mechanistic insights into their functioning. This review provides an overall understanding of the gut microbiome, its function, and communication with the brain and liver via the gut-brain axis and gut-liver axis. This review further discusses its role in some of the common disease states and some ways to potentially modulate the gut microbiome.

Background

Microbes are a community of organisms that reside and co-associate with the human body including a variety of organisms such as bacteria, viruses, and archaea (Turnbaugh et al., 2007). Once considered independent organisms, they are now considered to be an integral part of the human body that plays a role in health, and therefore sometimes also referred to as the 'forgotten organ' (O'Hara & Shanahan, 2006). Microbiome research has gained tremendous scientific interest over the past few decades with numerous studies being published each year. The Human Microbiome Project was launched in 2007 and supported by the National Institute of Health (NIH), to enable the characterization of the human microbiome to allow exploration of its role in health and disease (Turnbaugh et al., 2007).

Due to rapid growth in the field and the lack of a clear definition of the microbiome and its constituents, the microbiome has been defined in several ways e.g. driven by ecology or the microbes' habitat, based on microbe-host dependency, or by identification methods such as genome or DNA sequence-based analysis or their combination (Turnbaugh et al., 2007; Merriam-Webster Dictionary; Rogers & Zhang, 2016). Berg et al. (2020) recently provided a clear definition of microbiota and microbiome based on the description provided by Whipps (1988). They refer to the microbiome as an interactive microbial community, known as microbiota, in an environment that includes components such as structural elements and metabolites produced by microbial activity. The human microbiota is known to inhabit several organs including the gut, skin, mouth, nasal cavities, lungs, and vagina (Turnbaugh et al., 2007), and also refers to the collective genomes of existing microorganisms in these specific sites in the body.

This review provides an overview of the gut microbiome including its composition, detection methods, functions, communication with the brain and liver via the gut-brain axis and the gut-liver axis respectively, and potential ways of its modulation. As scientists explore this area of research and uncover more about the residents of the microbiome, this review is focused around its involvement in various biological functions and physiological changes that manifest in diseases. The crucial role of the gut microbiome can be seen with inflammatory bowel disease (IBD), a condition associated with an altered intestinal microbiota (Frank et al., 2007). A recent study by Britton et al. (2019) was performed in which they colonized germ-free mice with gut microbiota from

healthy individuals and those with IBD to elicit the role of the gut microbiome in IBD pathogenesis. The comparative analysis showed that the mice colonized with healthy microbiota displayed a significantly better immune response as shown by a higher number of regulatory T-cells, compared to the IBD colonized counterparts.

Microbiome Composition

Human microbiota consists of 10-100 trillion microorganisms, attributing approximately 1-3% of the body mass. This number is 10 times the number of human cells, compromises 100 times more genes than the human genome (O'Hara & Shanahan, 2006), and has metabolic activity equivalent to that of a human organ (Bocci, 1992). Multiple studies show that a well-balanced gut microbiome with constant interaction with the host immune system is essential for health (Round & Mazmanian, 2009; Clemente et al., 2012).

With age, a dynamic, interactive microbiome changes and is prone to various factors such as ecological and evolutionary changes which shape the microbial diversity (Ley et al., 2006). The fetal gut is sterile and colonization begins immediately after birth, influenced by the mode of delivery, and thereafter continues to change depending on various factors such as diet, environment, and medications (Ley et al., 2006). Gut microbial flora consists of bacteria from the four phyla, namely, Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria, with a lower proportion of the latter two (Ley et al., 2007). Anaerobes such as Bifidobacterium, Clostridium, Bacteroides, and Eubacteria, and aerobic bacteria including Escherichia, Enterococcus, Streptococcus, and Klebsiella constitute the majority of gut microbiota and contribute to its diversity (Eckburg et al., 2005). An increase in the ratio of Firmicutes⁄Bacteroidetes [F/B] with age and its association with gut dysbiosis has been reported (Mariat et al., 2009). This increased [F/B] ratio has been noted in disease states such as obesity and could be an indicator of host health (Indiani et al., 2018; Ley et al., 2006). According to some clinical studies, the microbial diversity may contribute to aging as it is significantly lower in older individuals compared to young adults, with a decrease in Bifidobacterium and Lactobacillus (Gavini et al., 2001; Odamaki et al., 2016; Forssten & Ouwehand, 2022). Decreased microbial diversity and richness have been implicated in the development of many age-related diseases such as colitis, cardiovascular and neurodegenerative disorders such as Alzheimer's and Parkinson's disease (Mitsuoka, 2014; Carding et al., 2015; Tang & Hazen, 2017; de J.R. De-Paula et al., 2018). A recent population study also reported the association of Type-2 Diabetes and insulin resistance with gut microbial diversity (Chen et al., 2021). Such evidence underscores the important role of microbiome diversity and richness in health and disease states.

Detection Methods

Detection of microbes became feasible with the introduction of phylogenetic markers such as the 16S rRNA gene for microbial community analysis (Woese & Fox, 1977). While scientific advancements have allowed the characterization of the microbiome in healthy individuals, there are still many microbes whose functions remain unknown and others that are yet to be detected. Conventional biochemical and molecular approaches to detection such as 16s rRNA, DNA microarrays, fluorescence in-situ hybridization (FISH), and quantitative real-time PCR (q-PCR) have enabled the detection of these microbes and thus enabled scientists to study and help understand the microbial functions and diversity.

Advancements in whole-genome sequencing including metagenomics, metaproteomics, metatranscriptomics, and metabolomics have also promoted the identification of novel genes and insights into their functional roles (Srivastava et al., 2019). Metagenomics, a DNA sequencing methodology involves coding the bacterial DNA sequences and annotating genes to provide a more comprehensive structural and functional role

for the microbial community. Metagenomics studies such as MetaHIT and American Human Microbiome Project have been able to add millions of non-redundant genes to the gene catalog of the human gut microbiome (HMPC, 2012; Kim et al., 2022). Furthermore, several studies have shown the functional involvement of metabolic pathways and their correlation to diseases using the -omics approach (Nicholson et al., 2005; Kim et al., 2022). These approaches have further advanced the understanding of microbial activity, gene expression, and role in metabolism. Interestingly, each individual has a specific microbial fingerprint which may therefore act as a determinant of an individual's risk of a certain disease (Tomasello et al., 2017). Such omics technologies could perform molecular fingerprinting of gut microbiota. It has become conceivable to identify novel genes and microbial functions that can be targeted for diagnostic purposes and be potentially used as a therapeutic tool for personalized medicine (Nicholson et al., 2005; Tomasello et al., 2017; Di Domenico et al., 2022).

Microbiome Function

Interaction between the host gut mucosa and the intestinal epithelium is critical in the establishment of a natural defense barrier, the development of the gut immune system, and metabolism. The microbiome has important protective, structural, and metabolic functions of the gut microbiome and their perturbation can result in disease states.

Protective Role

Maintenance of a symbiotic relationship promotes homeostatic balance and allows the growth of beneficial microbes and prevents the overgrowth of pathogenic microbes. The intestinal mucosal layer not only provides protection by preventing microbial contact with intestinal epithelial cells but also provides the microbes with nutrients in the form of secreted glycoproteins (Kim & Ho, 2010). Furthermore, metabolites generated by the microbes activate receptors such as Toll-like receptors (TLRs) and Nucleotide-binding and oligomerization domains (NOD) like receptors (NLRs). They also produce mucin glycoproteins, antimicrobial peptides, and local secretory IgA immunoglobulins whilst serving as signaling molecules (Schroeder & Bäckhed, 2016). Activation of these receptors can induce the signaling pathways essential for promoting mucosal barrier function and preventing gut inflammation (Macpherson & Uhr, 2004; Clemente et al., 2012). Indeed there is evidence that shows the ability of Lactobacillus reuteri to convert dietary histidine into histamine that modulates the downstream mitogen-activated protein kinase (MAPK) signaling pathway (Thomas et al., 2012). Collectively, these mechanisms prevent the translocation of the gut microbiota from the intestinal lumen to the circulation, sustain the microbes by providing nutrients for metabolic needs, and build up gut immunity. Such immune modulation can therefore be used to design treatment strategies against various diseases by targeting various signaling pathways.

Metabolic Role

A critical role of the microbiome lies in its profound influence on host metabolism including the metabolism of energy substrates, xenobiotics, synthesis of micronutrients like vitamins, and modulation of host immune defenses through the release of gut hormones such as cholecystokinin, glucagon-like peptide, and the peptide YY.

Energy Metabolism

Metabolic function of the microbes is dependent largely on the fermentation of dietary carbohydrates that escape digestion, non-digestible oligosaccharides, and also to a certain extent nutrients like glycoproteins secreted by the intestinal cells. This nutrient metabolism carried by the microbes in anoxic gut environment results in

the production of short-chain fatty acids like butyrate, propionate, and acetate, all of which are preferential energy sources for the host intestinal epithelium (O'Hara & Shanahan, 2006; Morrison & Preston, 2016). The short-chain fatty acids can be quickly oxidized to release high-energy molecules like Acetyl-CoA that participate in metabolic pathways and generate energy in the form of adenosine triphosphate (ATP). Additionally, studies show gut microbiota play a role in the metabolism of macronutrients, carbohydrates, lipids, and proteins. Members of Bacteroides express enzymes like transferases, hydrolases, and lyases that participate in carbohydrate metabolism, and modulate the activity of host lipid degrading enzymes like lipoprotein lipase (Ramakrishna, 2013). Similarly, protein metabolism is also impacted by microbial proteinases and peptidases along with host proteinases as they facilitate protein digestion and absorption (Rodríguez-Romero et al., 2022). Earlier studies have shown gut bacteria to be a source of essential amino acids such as lysine and threonine through de novo synthesis that contributes to amino acid homeostasis in the host (Metges, 2000). While amino acids and their metabolites are important drivers of normal physiological functions, accumulation of excessive undigested protein can result in a dysbiotic gut with an increased proportion of pathogenic microbes, rendering the host susceptible to diseases (Rodríguez-Romero et al., 2022).

Xenobiotics Metabolism

Yet another involvement of the gut microbiome concerns the metabolism of xenobiotics, substances that are not native to the host such as drugs, chemicals, food additives, environmental pollutants, and heavy metals (Collins & Patterson, 2020). Indeed, studies have identified bacterial genes of gut microbes to metabolize several drugs such as Levodopa used to treat Parkinson's disease, and Levamisole for parasitic infections (Zimmermann et al., 2019). While the direct metabolization of these substances involves the conversion of chemicals or drugs into inactive metabolites, the microbiome can alter the absorption of drugs and indirectly change their pharmacokinetics and pharmacodynamics by modulating the gene expression of host metabolic enzymes in the intestine and liver, including cytochrome P450, transporters and other conjugative enzymes (Maurice et al., 2013). Several such mechanisms employed by the gut microbiome on drug metabolism in clinical practice have also been noted in the literature (Sun et al., 2019). While the effect of gut microbes on xenobiotic metabolism is evident, the effect of xenobiotics on microbes should not be underestimated. The bidirectional interaction and binding and sequestration of xenobiotics by microbes can affect the viability, diversity, and metabolism of the microbiome as well.

Vitamin Synthesis

Besides providing an energy source for host cells, microbes are an excellent endogenous resource of micronutrients like vitamins (LeBlanc et al., 2013). Vitamins synthesized by gut commensal microbes include water-soluble B vitamins such as biotin, riboflavin, folate, thiamine, pantothenic acid, and fat-soluble Vitamin K, all of which can be utilized by the host cells (LeBlanc et al., 2013). Most water-soluble B-vitamins are critical in energy metabolism and serve as coenzymes in various redox reactions, and help stabilize the microbial community in the gut (Pham et al., 2021). Similarly, Vitamin K is critical for the activation of clotting factors and works as a free radical scavenger to protect our cells from oxidative damage. Phylloquinone and menaquinones, two different dietary forms of Vitamin K, are also produced and modulated by the gut microbiota (Bentley & Meganathan, 1982). Menaquinone also functions as a carrier in the bacterial electron transport system and quinone synthesis which are important for bacterial growth and survival (Fenn et al., 2017). The importance of having a healthy gut microbiome becomes important as an endogenous source of vitamins because the human body lacks the biosynthesis machinery to synthesize most vitamins and therefore relies on exogenous dietary sources.

Immune System Development

Another major role of the gut microbiome is its contribution to the development and modulation of gut immunity. Colonization of the gut in early life plays a critical role in the maturation of the host immune system and responses. This process usually lasts for ~ 3 years of age by which time the gut microbiome establishes itself in a newborn sterile gut and stabilizes to an adult-like gut environment and equipping the host with immunity (Gensollen et al., 2016). Hence, during the early years of life when the immune system is still immature, infants are highly susceptible to infectious pathogens that can result in disease states like allergies, and autoimmune and inflammatory disorders (Kamada et al., 2013; Zhang et al., 2017). While the non-optimal innate and adaptive responses of an immature immune system result in high susceptibility to infections, it also favors the immunoregulatory establishment of microbiota without severe inflammatory response (Kamada et al., 2013). Early studies by Bauer (1963) in germ-free animals demonstrate the absence of commensal microbes associated with defects in immune function. Similarly, literature affirms the association of microbial colonization with protective immunoglobulin A (IgA) antibodies that confer humoral immunity, innate lymphoid cells that mirror the phenotype and function of T-cells, and other immunomodulatory effector cells all contribute to immune responses (Gomez de Agüero et al., 2016). Various cytokines secreted by these cells also play important role in early immune responses to allergens, and bacterial and parasitic infections that have been proven with *in vivo* experiments in mice (Kamada et al., 2013; Hapfelmeier et al., 2010; Wesemann et al., 2013). Therefore, critical early life interactions between the host immune and microbiota are important to the establishment and maintenance of immune homeostasis and may impact susceptibility to infections and diseases later in life.

Gut Microbiome - Host Communication

Current literature describes an intricate network of the Gut microbiome and host communication through various organ systems including the liver and brain that impacts a myriad of biological and physiological functions (Clemente et al., 2012). While other organs such as the lungs, heart, and kidneys are reported to be affected by gut dysbiosis, in this review the focus is on gut communication with the brain and liver via the gut-brain axis and the gut-liver axis.

Gut-Brain Axis

Studies show the existence of bidirectional cross-talk between gut microbiota and host organ systems directly through the toll-like receptors (TLRs) or by indirect signaling through microbial metabolites (Schroeder & Bäckhed, 2016). Modulation of the gut-brain axis occurs through multiple pathways which include the endocrine, immune and neural systems. Under stress, the hypothalamic-pituitary-adrenal axis (HPA axis) regulates the cortisol secretion from the adrenal gland in response to the sequential release of corticotropin hormone (CRH) secreted by the hypothalamus and adrenocorticotropic hormone (ACTH) released by the pituitary gland (Misiak et al., 2020). Cortisol in turn affects the immune cells and modulates the gut permeability and intestinal barrier integrity, all of which can change the gut environment and consequently alter the microbiota composition (Morais et al., 2020). As such the dysbiotic gut-brain communication and aberrant signaling further results in abnormal brain physiology and perturbed function seen in the form of signs and symptoms such as increased stress, pain, anxiety, cognition, mood changes, inflammation, and diseases. Further, microbial interaction with the host immune cells initiates the production of pro-inflammatory cytokines that can reach the brain via blood circulation and alter brain function. Inflammation affects the intestinal permeability rendering the gut 'leaky' causing intestinal dysbiosis which is recognized to be associated with metabolic disorders (Régnier et al., 2021). Early studies by Cani et al. provide evidence that the bacterial lipopolysaccharide is capable of triggering endotoxemia-mediated inflammation and participates in the development of insulin resistance (2007).

The gut, also known as the 'second brain', produces and consumes many of the same neurotransmitters as the brain including dopamine, serotonin, norepinephrine, histamine, and gamma-aminobutyric acid (GABA) (Strandwitz, 2018). A significant amount of serotonin is produced by the gut bacteria that contribute to anxiety

and changes in mood, and behavior. Serotonin is known to exhibit antioxidant, and anti-inflammatory properties, besides serving as a precursor to melatonin, a chemical known to regulate circadian rhythm and the sleep cycle. Literature provides the linkage of the role of melatonin and the gut-brain axis not just with sleep physiology, but also with psychiatric, inflammatory, and neurodegenerative disorders (Anderson & Maes, 2015). Further, the proinflammatory cytokines such as interleukins, in particular, IL-6 and IL-1β are somnogenic factors that have been found to have a strong association with sleep physiology (Kamada et al., 2013). Other microbial metabolites such as short-chain fatty acids and tryptophan metabolites serve as precursors for neurotransmitters like glutamate, GABA, and dopamine that modulate the synaptic transmission in the enteric nervous system, regulate intestinal motility, secretion and inflammation, energy intake, and thermal homeostasis (Auteri et al., 2015; de J.R. De-Paula et al., 2018; Ge et al., 2018).

Besides the enteric nervous system, the gut-brain axis uses other pathways that involve hormones for communication and monitoring various stimuli and signals from the gut. The specialized enteroendocrine cells present throughout the intestinal tract release hormones such as cholecystokinin (CCK), glucagon-like peptide-1 (GLP-1), and peptide YY (PYY), in direct response to nutrients and microbial factors (Cani & Knauf, 2016). These hormones secreted due to gut-brain interaction control various functions such as regulation of appetite, gastric emptying, and secretion of pancreatic enzymes responsible for carbohydrate, protein, and lipid metabolism (Covasa et al., 2019; Owyang & Logsdon, 2004; Ritter, 2004). In addition, recent literature reports that gut sensory epithelial cells or neuropods are an emerging player involved in the transduction of sensory signals through an existing neuronal network from the gut, vagus nerve, and the brain (Kaelberer et al., 2020). A 2018 study by Breit et al. affirms that the vagus nerve is a modulator of the gut-brain axis in psychiatric and inflammatory disorders. Thus, manipulation and regulation of microbiota-derived neuroactive metabolites may be of strategic value in the treatment of many endocrinal, intestinal and neurological disorders.

Gut-Liver Axis

The gut-liver axis is another cross-talk mechanism that exists as a result of interactions affected by different dietary, genetic, and environmental factors and affects the functional and physiological body responses. The main component of the gut liver axis is the portal circulation that directs the venous blood away from the intestine. Any damage to the gut barrier can therefore result in increased intestinal permeability and expose the liver to potentially harmful substances, gut bacteria, and their toxic metabolites (Brandl et al., 2017). Additionally, any dysbiosis due to alteration in microbial diversity and richness can further exaggerate this process of liver damage and disease by altering the bile-acid metabolism (Betrapally et al., 2017). Literature provides increasing evidence of the role of intestinal dysbiosis in the pathogenesis and progression of liver diseases such as alcoholic liver disease (ALD), non-alcoholic fatty liver disease (NAFLD), cirrhosis, immune-mediated diseases, and cancer. A study conducted on patients suffering from hepatocellular carcinoma showed a dramatic decrease in the diversity of gut microbes as compared to healthy subjects (Ponziani et al., 2018). An increase in the pro-inflammatory Bacteroides species and decreased levels of anti-inflammatory Bifidobacterium were noted to be a likely cause contributing to the progression of carcinogenesis. The role of gut dysbiosis has also been implicated in the pathogenesis of autoimmune diseases such as biliary cirrhosis where the portal inflammation due to toxic bacterial metabolites and change in bile acid composition progressively leads to fibrosis and cirrhosis. A recent study by Tang et al. (2018) demonstrated a correlation between reduced gut microbial diversity and richness to primary biliary cirrhosis. The link of the gut microbiome to Alcoholic liver disease (ALD) has long been associated with alcohol-mediated damage to intestinal cells that results in increased gut permeability and eventual hepatic injury and inflammation (Cassard & Ciocan, 2018). This finding is currently supported by meta-analysis studies in patients with chronic liver disease which showed an imbalance in the native bacterial species (Shah et al., 2017). Similar to ALD, the progression and pathogenesis of the non-alcoholic fatty liver disease (NAFLD) to liver cirrhosis and hepatocellular carcinoma is linked to intestinal dysbiosis (Doulberis et al., 2017).

Modulating the Gut Microbiome

Considering the significant role of the microbiome in overall health and its association with various disease states, it is only rational to explore the ways to target the gut microbiota as a therapeutic strategy. With emerging concepts and technological advances, the development of diagnostic, prognostic, and therapeutic tools to modulate the gut microbiota for the management of diseases seems feasible, however, challenges should be expected in this new field of scientific research (Ghattargi et al., 2019; Sarada et al., 2021).

Since diet plays a major role in the constitution of the gut microbiome and is an influential modulator of the gut microbiota, the role of probiotics, prebiotics, postbiotics, and synbiotics has been investigated (Liu et al., 2022). Additionally, fecal microbiota transplantation (FMT) is currently being explored as a therapeutic strategy for several diseases. All these modulators are further described below.

Probiotics are live microorganisms intended for health benefit upon consumption and are commonly found in yogurt, other fermented foods, and dietary supplements. Most common probiotic bacteria belong to the Lactobacillus and Bifidobacterium groups and are suggested to maintain microbial homeostasis in the gut and prevent the colonization of pathogenic bacteria. The mechanism of action of probiotics is multifold and includes inhibition of colonization of pathogenic bacteria by releasing antimicrobial peptides or bacteriocins. They further confer resistance to colonization by competing for nutrients and space by adhering to intestinal cells (Liu et al., 2022; Sherman et al., 2009). The distinct immunomodulatory effect of probiotics on immune cells also helps reduce colonic inflammation. Probiotics can shift the gut microbial community towards the more beneficial microbes that produce anti-inflammatory metabolites that promote the differentiation of anti-inflammatory immune regulatory T-cells (Tregs) and inhibit the T-helper 17 (Th17) that produce highly inflammatory IL-17 cytokines (Sherman et al., 2009; Tanabe, 2013). Finally, probiotics interact with intestinal mucosa to promote mucin production and therefore prevent a leaky gut and endotoxemia by preventing bacterial translocation to the systemic circulation (Sherman et al., 2009).

Prebiotics are dietary supplements consisting of non-absorbable fermentable dietary fibers (Holscher, 2017). They function by stimulating the growth of beneficial probiotic bacteria. Studies report the increase in probiotic bacteria such as Faecalibacterium and Akkermansia after the administration of prebiotics (Zou et al., 2020; Liu et al., 2022). They also are selectively fermented by probiotic bacteria in the gut, leading to the synthesis of short-chain fatty acids (SCFAs) such as acetate, propionate, and butyrate, which can be used by intestinal cells for energy (Zou et al., 2020; Liu et al., 2022). Further, prebiotics can inhibit pathogen colonization by binding to bacterial receptors, thus preventing the attachment of pathogens to the intestinal cells (Zou et al., 2020). Prebiotics has also been postulated to be directly absorbed into the intestinal cells and exert anti-inflammatory action (Liu et al., 2022).

Postbiotics are the soluble byproducts and metabolites secreted by the gut microbiota and can help maintain intestinal homeostasis by inhibiting the pathogenic bacteria while promoting the growth of beneficial ones. The interferons and Immunoglobulin A are postbiotics that exert biological activities to protect the intestinal epithelium and exert cytotoxic effect against aberrant cells to induce apoptosis (Zou et al., 2020; Liu et al., 2022). Studies show that postbiotics can promote the integrity of the intestinal barrier by increasing the expression of tight junction proteins such as Occludin and Claudin-1, the antioxidant enzymes such as superoxide dismutase, and the mucin in intestinal epithelial cells (Izuddin et al., 2020). Postbiotics may also interact with several immune cells such as T-cells, B-cells, macrophages, and dendritic cells to exert an effect on the immune system and immune response (Liu et al., 2022).

Fecal Microbiota Transplantation (FMT), also known as intestinal microbiota transplant or bacteriotherapy, is another way to modulate the gut microbiota. The process works by transplanting fecal samples from screened healthy donors to the colon of the recipient. The U.S. FDA approved FMT as an investigational treatment and was successfully used for treating patients with recurrent, severe Clostridium difficile infection that

causes colitis or colon inflammation leading to diarrhea (FDA, 2016; Burke & Lamont, 2014). This therapeutic technique can re-establish the gut microenvironment to modulate the enteric and systemic immunity. Studies in patients with metabolic syndrome show that FMT is able to improve insulin sensitivity most likely by altering the microbiota in favor of beneficial butyrate-producing bacteria (Udayappan et al., 2014). There is significant interest in the use of FMT for other diseases such as colorectal cancer (CRC), inflammatory bowel disease (IBD), obesity, and liver disease (Smits et al., 2013). A recent study conducted preliminary human trials showed beneficial effects of FMT in patients with severe alcoholic hepatitis with improvement in disease severity and survival rate (Shasthry, 2020). Ongoing research and clinical trials continue to explore the use of FMT to restore normobiosis in different pathological situations characterized by dysbiosis (Smits et al., 2013). However, it is important to note that the impact of FMT may vary for each individual and is not without risks. Such risks include the dissemination of pathogens and disease-causing genes from recipients and unknown long-term effects.

Conclusion

The gut microbiome is a complex but integral part of the human body. While research in the field has furthered our knowledge and understanding of this field, a lot remains to be uncovered about the gut microbiome. Some of the critical established roles of the gut microbiome lie within its protective and anti-microbial function and metabolic regulation. Research further underscores its important communication role through its cross-talk with other organs such as the brain and liver via the gut-brain and gut-liver axis, which when perturbed may result in disease states. The technological advancements and methodologies in whole-genome sequencing such as metagenomics, metaproteomics, metatranscriptomics, and metabolomics have allowed the identification of novel genes and provided valuable information on the functional roles and mechanistic insights. With the possibility of creating individual microbiome profiles, such information could be potentially useful in personalized medicine where treatment can be designed for specific individuals. While the use of probiotics, prebiotics, postbiotics, and synbiotics are common ways to modulate the gut microbiome, another interesting option is the use of fecal microbiota transplant (FMT). FMT is currently a treatment option for Clostridium difficile infections and is being explored as a potential therapeutic strategy in clinical trials. With ongoing research and innovative techniques, gut microbiome manipulation could prove to be a revolutionary way to target various diseases.

Acknowledgments

I would like to thank my advisor for the valuable insight provided to me on this topic.

References

Anderson, G., & Maes, M. (2015). The gut–brain axis: The role of melatonin in linking psychiatric, inflammatory and neurodegenerative conditions. *Advances in Integrative Medicine*, *2*(1), 31–37. https://doi.org/10.1016/j.aimed.2014.12.007

Auteri, M., Zizzo, M. G., & Serio, R. (2015). GABA and GABA receptors in the gastrointestinal tract: From motility to inflammation. *Pharmacological Research*, *93*, 11–21. https://doi.org/10.1016/j.phrs.2014.12.001

Bauer, H., Horowitz, R. E., Lewensen, S. M., & Popper, H. (1963). Response of the lymphatic tissue to the microbial flora. Studies on germ free mice. *Am. J. Pathol*, *42*, 471–483.

Bentley, R., & Meganathan, R. (1982). Biosynthesis of vitamin K (menaquinone) in bacteria. *Microbiological Reviews*, *46*(3), 241–280. https://doi.org/10.1128/mr.46.3.241-280.1982

Berg, G., Rybakova, D., Lima, N., Loy, A., Macklin, J. A., Maguin, E., Mauchline, T., McClure, R., Schloter, M. (2020). Microbiome definition re-visited: Old concepts and new challenges. *Microbiome*, *8*(1). https://doi.org/10.1186/s40168-020-00875-0

Betrapally, N. S., Gillevet, P. M., & Bajaj, J. S. (2017). Gut microbiome and liver disease. *Translational Research*, *179*, 49–59. https://doi.org/10.1016/j.trsl.2016.07.005

Bocci, V. (1992). The neglected organ: Bacterial Flora has a crucial immunostimulatory role. *Perspectives in Biology and Medicine*, *35*(2), 251–260. https://doi.org/10.1353/pbm.1992.0004

Brandl, K., Kumar, V., & Eckmann, L. (2017). Gut-liver axis at the frontier of host-microbial interactions. *American Journal of Physiology-Gastrointestinal and Liver Physiology*, *312*(5). https://doi.org/10.1152/ajpgi.00361.2016

Breit, S., Kupferberg, A., Rogler, G., & Hasler, G. (2018). Vagus nerve as modulator of the brain–gut axis in psychiatric and inflammatory disorders. *Frontiers in Psychiatry*, *9*. https://doi.org/10.3389/fpsyt.2018.00044

Britton, G. J., Contijoch, E. J., Clemente, J. C., Grinspan, A., Sands, B. E., Colombel, J.-F., … Faith, J. J. (2019). Microbiotas from humans with inflammatory bowel disease alter the balance of gut th17 and rorγt+ regulatory T cells and exacerbate colitis in mice. *Immunity*, *50*(1). https://doi.org/10.1016/j.immuni.2018.12.015

Burke, K. E., & Lamont, J. T. (2014). *clostridium difficile* infection: A worldwide disease. *Gut and Liver*, *8*(1), 1–6. https://doi.org/10.5009/gnl.2014.8.1.1

Cani, P. D., & Knauf, C. (2016). How gut microbes talk to organs: The role of endocrine and nervous routes. *Molecular Metabolism*, *5*(9), 743–752. https://doi.org/10.1016/j.molmet.2016.05.011

Cani, P. D., Amar, J., Iglesias, M, Chamontin, B., Ferrières Jean, Tanti Jean-François, Gibson, G. R., Casteilla, L., … Burcelin Rémy. (2007). Metabolic endotoxemia initiates obesity and insulin resistance. *Diabetes*, *56*(7), 1761–1772. https://doi.org/10.2337/db06-1491

Carding, S., Verbeke, K., Vipond, D. T., Corfe, B. M., & Owen, L. J. (2015). Dysbiosis of the gut microbiota in disease. *Microbial Ecology in Health & Disease*, *26*. https://doi.org/10.3402/mehd.v26.26191

Cassard, A.-M., & Ciocan, D. (2018). Microbiota, a key player in alcoholic liver disease. *Clinical and Molecular Hepatology*, *24*(2), 100–107. https://doi.org/10.3350/cmh.2017.0067

Chen, Z., Radjabzadeh, D., Uitterlinden, A. G., Zhernakova, A., Fu, J., Kraaij, R., & Voortman, T. (2021). Association of insulin resistance and type 2 diabetes with gut microbial diversity. *JAMA Network Open*, *4*(7). https://doi.org/10.1001/jamanetworkopen.2021.18811

Clemente, J. C., Ursell, L. K., Parfrey, L. W., & Knight, R. (2012). The impact of the gut microbiota on human health: An integrative view. *Cell*, *148*(6), 1258–1270. https://doi.org/10.1016/j.cell.2012.01.035

Collins, S. L., & Patterson, A. D. (2020). The gut microbiome: An orchestrator of xenobiotic metabolism. *Acta Pharmaceutica Sinica B*, *10*(1), 19–32. https://doi.org/10.1016/j.apsb.2019.12.001

Covasa, M., Stephens, R. W., Toderean, R., & Cobuz, C. (2019). Intestinal sensing by gut microbiota: Targeting gut peptides. *Frontiers in Endocrinology*, *10*. https://doi.org/10.3389/fendo.2019.00082

de J.R. De-Paula, V., Forlenza, A. S., & Forlenza, O. V. (2018). Relevance of gut microbiota in cognition, behaviour and alzheimer's disease. *Pharmacological Research*, *136*, 29–34. https://doi.org/10.1016/j.phrs.2018.07.007

Di Domenico, M., Ballini, A., Boccellino, M., Scacco, S., Lovero, R., Charitos, I. A., & Santacroce, L. (2022). The intestinal microbiota may be a potential theranostic tool for personalized medicine. *Journal of Personalized Medicine*, *12*(4), 523. https://doi.org/10.3390/jpm12040523

Doulberis, M., Kotronis, G., Gialamprinou, D., Kountouras, J., & Katsinelos, P. (2017). Non-alcoholic fatty liver disease: An update with special focus on the role of gut microbiota. *Metabolism*, *71*, 182–197. https://doi.org/10.1016/j.metabol.2017.03.013

Eckburg, P. B., Bik, E. M., Bernstein, C. N., Purdom, E., Dethlefsen, L., Sargent, M., Gill, S. R., Nelson, K. E., & Relman, D. A. (2005). Diversity of the human intestinal microbial flora. *Science*, *308*(5728), 1635–1638. https://doi.org/10.1126/science.1110591

Fenn, K., Strandwitz, P., Stewart, E. J., Dimise, E., Rubin, S., Gurubacharya, S., Clardy, J., & Lewis, K. (2017). Quinones are growth factors for the human gut microbiota. *Microbiome*, *5*(1). https://doi.org/10.1186/s40168-017-0380-5

Forssten, S. D., & Ouwehand, A. C. (2022). Contribution of the microbiota to Healthy Aging. *Comprehensive Gut Microbiota*, 69–84. https://doi.org/10.1016/b978-0-12-819265-8.00059-0

Framework for human microbiome research. (2012). *Nature*, *486*(7402), 215–221. https://doi.org/10.1038/nature11209

Frank, D. N., St. Amand, A. L., Feldman, R. A., Boedeker, E. C., Harpaz, N., & Pace, N. R. (2007). Molecular-phylogenetic characterization of microbial community imbalances in human inflammatory bowel diseases. *Proceedings of the National Academy of Sciences*, *104*(34), 13780–13785. https://doi.org/10.1073/pnas.0706625104

Gavini, F., Cayuela, C., & Neut, C. (2001). Differences in the distribution of bifidobacterial and enterobacterial species in human faecal microflora of three different (children, adults, elderly) age groups. *Microbial Ecology in Health and Disease*, *13*(1), 40–45. https://doi.org/10.1080/089106001750071690

Ge, X., Pan, J., Liu, Y., Wang, H., Zhou, W., & Wang, X. (2018). Intestinal crosstalk between microbiota and serotonin and its impact on Gut Motility. *Current Pharmaceutical Biotechnology*, *19*(3), 190–195. https://doi.org/10.2174/1389201019666180528094202

Gensollen, T., Iyer, S. S., Kasper, D. L., & Blumberg, R. S. (2016). How colonization by Microbiota in early life shapes the immune system. *Science*, *352*(6285), 539–544. https://doi.org/10.1126/science.aad9378

Ghattargi, V. C., Sape, K., Kumbhare, S. V., & Shouche, Y. S. (2019). Mining human microbiome for therapeutics. *Microbial Diversity in Ecosystem Sustainability and Biotechnological Applications*, 573–613. https://doi.org/10.1007/978-981-13-8315-1_18

Gomez de Agüero, M., Hapfelmeier, S., Sauer, U., McCoy, K. D., & Macpherson, A. J. (2016). The maternal microbiota drives early postnatal innate immune development. *Science*, *351*(6279), 1296–1302. https://doi.org/10.1126/science.aad2571

Hapfelmeier, S., Lawson, M. A., Velykoredko, Y., Balmer, M. L., Endt, K., Geuking, M. B., Curtiss, R., McCoy, K. D., & Macpherson, A. J. (2010). Reversible microbial colonization of germ-free mice reveals the dynamics of Iga Immune Responses. *Science*, *328*(5986), 1705–1709. https://doi.org/10.1126/science.1188454

Holscher, H. D. (2017). Dietary fiber and prebiotics and the gastrointestinal microbiota. *Gut Microbes*, *8*(2), 172–184. https://doi.org/10.1080/19490976.2017.1290756

Indiani, C. M., Rizzardi, K. F., Castelo, P. M., Ferraz, L. F., Darrieux, M., & Parisotto, T. M. (2018). Childhood obesity and Firmicutes/bacteroidetes ratio in the gut microbiota: A systematic review. *Childhood Obesity*, *14*(8), 501–509. https://doi.org/10.1089/chi.2018.0040

Izuddin, W. I., Humam, A. M., Loh, T. C., Foo, H. L., & Samsudin, A. A. (2020). Dietary postbiotic lactobacillus plantarum improves serum and ruminal antioxidant activity and upregulates hepatic antioxidant enzymes and ruminal barrier function in post-weaning lambs. *Antioxidants*, *9*(3), 250. https://doi.org/10.3390/antiox9030250

Kaelberer, M. M., Rupprecht, L. E., Liu, W. W., Weng, P., & Bohórquez, D. V. (2020). Neuropod cells: The emerging biology of gut-brain sensory transduction. *Annual Review of Neuroscience*, *43*(1), 337–353. https://doi.org/10.1146/annurev-neuro-091619-022657

Kamada, N., Seo, S.-U., Chen, G. Y., & Núñez, G. (2013). Role of the gut microbiota in immunity and inflammatory disease. *Nature Reviews Immunology*, *13*(5), 321–335. https://doi.org/10.1038/nri3430

Kim, C. Y., Ma, J., & Lee, I. (2022). HiFi metagenomic sequencing enables assembly of accurate and complete genomes from human gut microbiota. https://doi.org/10.1101/2022.02.09.479829

Kim, Y. S., & Ho, S. B. (2010). Intestinal goblet cells and mucins in health and disease: Recent insights and progress. *Current Gastroenterology Reports*, *12*(5), 319–330. https://doi.org/10.1007/s11894-010-0131-2

LeBlanc, J. G., Milani, C., de Giori, G. S., Sesma, F., van Sinderen, D., & Ventura, M. (2013). Bacteria as vitamin suppliers to their host: A gut microbiota perspective. *Current Opinion in Biotechnology*, *24*(2), 160–168. https://doi.org/10.1016/j.copbio.2012.08.005

Ley, R. E., Knight, R., & Gordon, J. I. (2007). The human microbiome: Eliminating the biomedical/environmental dichotomy in Microbial Ecology. *Environmental Microbiology*, *9*(1), 3–4. https://doi.org/10.1111/j.1462-2920.2006.01222_3.x

Ley, R. E., Peterson, D. A., & Gordon, J. I. (2006). Ecological and evolutionary forces shaping microbial diversity in the human intestine. *Cell*, *124*(4), 837–848. https://doi.org/10.1016/j.cell.2006.02.017

Ley, R. E., Turnbaugh, P. J., Klein, S., & Gordon, J. I. (2006). Human gut microbes associated with obesity. *Nature*, *444*(7122), 1022–1023. https://doi.org/10.1038/4441022a

Liu, Y., Wang, J., & Wu, C. (2022). Modulation of gut microbiota and immune system by probiotics, pre-biotics, and post-biotics. *Frontiers in Nutrition*, *8*. https://doi.org/10.3389/fnut.2021.634897

Macpherson, A. J., & Uhr, T. (2004). Induction of protective IGA by intestinal dendritic cells carrying commensal bacteria. *Science*, *303*(5664), 1662–1665. https://doi.org/10.1126/science.1091334

Mariat, D., Firmesse, O., Levenez, F., Guimarães, V. D., Sokol, H., Doré, J., Corthier, G., & Furet, J.-P. (2009). The Firmicutes/bacteroidetes ratio of the human microbiota changes with age. *BMC Microbiology*, *9*(1), 123. https://doi.org/10.1186/1471-2180-9-123

Maurice, C. F., Haiser, H. J., & Turnbaugh, P. J. (2013). Xenobiotics shape the physiology and gene expression of the active human gut microbiome. *Cell*, *152*(1-2), 39–50. https://doi.org/10.1016/j.cell.2012.10.052

Merriam-Webster. (n.d.). *Microbiome definition & meaning*. Merriam-Webster. Retrieved June 22, 2022, from https://www.merriam-webster.com/dictionary/microbiome

Metges, C. C. (2000). Contribution of microbial amino acids to amino acid homeostasis of the host. *The Journal of Nutrition*, *130*(7). https://doi.org/10.1093/jn/130.7.1857s

Misiak, B., Łoniewski, I., Marlicz, W., Frydecka, D., Szulc, A., Rudzki, L., & Samochowiec, J. (2020). The HPA axis dysregulation in severe mental illness: Can we shift the blame to gut microbiota? *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *102*, 109951. https://doi.org/10.1016/j.pnpbp.2020.109951

Mitsuoka, T. (2014). Decline in Microbial Diversity and Richness of the Microbiome with Age. *Biosci.Microbiota Food Health*, *33*, 99–116.

Morais, L. H., Schreiber, H. L., & Mazmanian, S. K. (2020). The gut microbiota–brain axis in behaviour and brain disorders. *Nature Reviews Microbiology*, *19*(4), 241–255. https://doi.org/10.1038/s41579-020-00460-0

Morrison, D. J., & Preston, T. (2016). Formation of short chain fatty acids by the gut microbiota and their impact on human metabolism. *Gut Microbes*, *7*(3), 189–200. https://doi.org/10.1080/19490976.2015.1134082

Nicholson, J. K., Holmes, E., & Wilson, I. D. (2005). Gut microorganisms, mammalian metabolism and personalized health care. *Nature Reviews Microbiology*, *3*(5), 431–438. https://doi.org/10.1038/nrmicro1152

Odamaki, T., Kato, K., Abe, F., & Osawa, R. (2016). Age-related changes in gut microbiota composition from newborn to Centenarian: A cross-sectional study. *BMC Microbiology*, *16*(1). https://doi.org/10.1186/s12866-016-0708-5

O'Hara, A. M., & Shanahan, F. (2006). The gut flora as a forgotten organ. *EMBO Reports*, *7*(7), 688–693. https://doi.org/10.1038/sj.embor.7400731

Owyang, C., & Logsdon, C. D. (2004). New insights into neurohormonal regulation of pancreatic secretion. *Gastroenterology*, *127*(3), 957–969. https://doi.org/10.1053/j.gastro.2004.05.002

Pham,V. T., Dold, S., Rehman, A., Bird, J. K., & Steinert, R. E. (2021). Vitamins, the gut microbiome and gastrointestinal health in humans. *Nutrition Research*, *95*, 35–53. https://doi.org/10.1016/j.nutres.2021.09.001

Ponziani, F. R., Bhoori, S., Calvani, R., Camisaschi, C., Picca, A., Tuccitto, A., Gasbarrini, A., Pompili, M., & Mazzaferro, V. (2018). Hepatocellular carcinoma is associated with gut microbiota profile and inflammation in nonalcoholic fatty liver disease. *Hepatology*, *69*(1), 107–120. https://doi.org/10.1002/hep.30036

Ramakrishna, B. S. (2013). Role of the gut microbiota in human nutrition and metabolism. *Journal of Gastroenterology and Hepatology*, *28*, 9–17. https://doi.org/10.1111/jgh.12294

Ritter, R. C. (2004). Gastrointestinal mechanisms of satiation for food. *Physiology & Behavior*, *81*(2), 249–273. https://doi.org/10.1016/j.physbeh.2004.02.012

Rodríguez-Romero, J. de, Durán-Castañeda, A. C., Cárdenas-Castro, A. P., Sánchez-Burgos, J. A., Zamora-Gasga, V. M., & Sáyago-Ayerdi, S. G. (2022). What we know about protein gut metabolites: Implications and insights for human health and diseases. *Food Chemistry: X*, *13*, 100195. https://doi.org/10.1016/j.fochx.2021.100195

Rogers, Y.-H., & Zhang, C. (2016). Genomic Technologies in Medicine and Health. *Medical and Health Genomics*, 15–28. https://doi.org/10.1016/b978-0-12-420196-5.00002-2

Round, J. L., & Mazmanian, S. K. (2009). The gut microbiota shapes intestinal immune responses during health and disease. *Nature Reviews Immunology*, *9*(5), 313–323. https://doi.org/10.1038/nri2515

Régnier, M., Hul, M. V., Knauf, C., & Cani, P. D. (2021). Gut microbiome, endocrine control of gut barrier function and Metabolic Diseases. *Journal of Endocrinology*, *250*(1). https://doi.org/10.1530/joe-20-0473e

Sarada, J., Anju, S., Aparna, Y., & Anuradha, K. (2021). Microbiome therapeutics: Emerging concepts and challenges. *Microbiome in Human Health and Disease*, 217–238. https://doi.org/10.1007/978-981-16-3156-6_11

Schroeder, B. O., & Bäckhed, F. (2016). Signals from the gut microbiota to distant organs in physiology and disease. *Nature Medicine*, *22*(10), 1079–1089. https://doi.org/10.1038/nm.4185

Shah, A., Shanahan, E., Macdonald, G., Fletcher, L., Ghasemi, P., Morrison, M., Jones, M., & Holtmann, G. (2017). Systematic Review and meta-analysis: Prevalence of small intestinal bacterial overgrowth in chronic liver disease. *Seminars in Liver Disease*, *37*(04), 388–400. https://doi.org/10.1055/s-0037-1608832

Shasthry, S. M. (2020). Fecal microbiota transplantation in alcohol related liver diseases. *Clinical and Molecular Hepatology*, *26*(3), 294–301. https://doi.org/10.3350/cmh.2020.0057

Sherman, P. M., Ossa, J. C., & Johnson-Henry, K. (2009). Unraveling mechanisms of action of probiotics. *Nutrition in Clinical Practice*, *24*(1), 10–14. https://doi.org/10.1177/0884533608329231

Smits, L. P., Bouter, K. E. C., de Vos, W. M., Borody, T. J., & Nieuwdorp, M. (2013). Therapeutic potential of fecal microbiota transplantation. *Gastroenterology*, *145*(5), 946–953. https://doi.org/10.1053/j.gastro.2013.08.058

Srivastava, N., Gupta, B., Gupta, S2012., Danquah, M. K., & Sarethy, I. P. (2019). Analyzing functional microbial diversity. *Microbial Diversity in the Genomic Era*, 79–102. https://doi.org/10.1016/b978-0-12-814849-5.00006-x

Strandwitz, P. (2018). Neurotransmitter modulation by the gut microbiota. *Brain Research*, *1693*, 128–133. https://doi.org/10.1016/j.brainres.2018.03.015

Sun, C., Chen, L., & Shen, Z. (2019). Mechanisms of gastrointestinal microflora on drug metabolism in clinical practice. *Saudi Pharmaceutical Journal*, *27*(8), 1146–1156. https://doi.org/10.1016/j.jsps.2019.09.011

Tanabe, S. (2013). The effect of probiotics and gut microbiota on th17 cells. *International Reviews of Immunology*, *32*(5-6), 511–525. https://doi.org/10.3109/08830185.2013.839665

Tang, R., Wei, Y., Xiao, X., Fan, Z., Wu, M., Qiu, D., Fang, J.-Y., Ansari, A, Ma, X. (2017). Gut microbial profile is altered in primary biliary cholangitis and partially restored after UDCA therapy. *Gut*, *67*(3), 534–541. https://doi.org/10.1136/gutjnl-2016-313332

Tang, W. H., & Hazen, S. L. (2017). The gut microbiome and its role in cardiovascular diseases. *Circulation*, *135*(11), 1008–1010. https://doi.org/10.1161/circulationaha.116.024251

Thomas, C. M., Hong, T., Hu, W., Britton, R. A., Kalkum, M., & Versalovic, J. (2012). Histamine derived from probiotic lactobacillus reuteri suppresses TNF via modulation of PKA and Erk Signaling. *PLoS ONE*, *7*(2). https://doi.org/10.1371/journal.pone.0031951

Tomasello, G., Mazzola, M., Jurjus, A., Carini, F., Damiani, P., Geagea, A. G., Zeeny, M. N., & Leone, A. (2017). The fingerprint of the human gastrointestinal tract microbiota: a hypothesis of molecular mapping. *J. Biol Regul Homeost Agents 31*(1), 245–249.

Turnbaugh, P. J., Ley, R. E., Hamady, M., Fraser-Liggett, C. M., Knight, R., & Gordon, J. I. (2007). The Human Microbiome Project. *Nature*, *449*(7164), 804–810. https://doi.org/10.1038/nature06244

Udayappan, S. D., Hartstra, A. V., Dallinga-Thie, G. M., & Nieuwdorp, M. (2014). Intestinal microbiota and faecal transplantation as treatment modality for insulin resistance and type 2 diabetes mellitus. *Clinical and Experimental Immunology*, *177*(1), 24–29. https://doi.org/10.1111/cei.12293

U.S. Food and Drug Administration. (2016) *Use of fecal microbiota for transplantation (FMT) to treat clostridium.*. Retrieved from https://www.fda.gov/news-events/fda-meetings-conferences-and-workshops/use-fecal-microbiota-transplantation-fmt-treat-clostridium-difficile-infection-not-responsive

Wesemann, D. R., Portuguese, A. J., Magee, J. M., Panchakshari, R. A., Rodig, S. J., Kepler, T. B., & Alt, F. W. (2013). Microbial colonization influences early B-lineage development in the gut lamina propria. *Nature*, *501*(7465), 112–115. https://doi.org/10.1038/nature12496

Whipps, J. M. (n.d.). Mycoparasitism and plant disease control. In N. Burge (Ed.), *Fungi Biol Control Syst.* (pp. 161–187). Essay, Manchester: Manchester University Press.

Woese, C. R., & Fox, G. E. (1977). Phylogenetic structure of the prokaryotic domain: The primary kingdoms. *Proceedings of the National Academy of Sciences*, *74*(11), 5088–5090. https://doi.org/10.1073/pnas.74.11.5088

Zhang, X., Zhivaki, D., & Lo-Man, R. (2017). Unique aspects of the perinatal immune system. *Nature Reviews Immunology*, *17*(8), 495–507. https://doi.org/10.1038/nri.2017.54

Zimmermann, M., Zimmermann-Kogadeeva, M., Wegmann, R., & Goodman, A. L. (2019). Mapping human microbiome drug metabolism by gut bacteria and their genes. *Nature*, *570*(7762), 462–467. https://doi.org/10.1038/s41586-019-1291-3

Zou, Y., Wang, J., Lv, H., & Wang, S. (2020). Protection of galacto-oligosaccharide against E. coli O157 colonization through enhancing gut barrier function and modulating gut microbiota. *Foods*, *9*(11), 1710. https://doi.org/10.3390/foods9111710