Gut Microbial Dysbiosis in the Pathogenesis of Gastrointestinal Dysmotility and Metabolic Disorders

Rajan Singh,¹ Hannah Zogg,¹ Lai Wei,¹ Allison Bartlett,¹ Uday C Ghoshal,²,* Singh Rajender,³ and Seungil Ro¹*  

¹Department of Physiology and Cell Biology, University of Nevada School of Medicine, Reno, NV, USA; ²Department of Gastroenterology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India; and ³Department of Endocrinology, Central Drug Research Institute, Lucknow, India

Of all microorganisms in the human body, the largest and most complex population resides in the gastrointestinal (GI) tract. The gut microbiota continuously adapts to the host environment and serves multiple critical functions for their hosts, including regulating host immunity, procuring energy from food, and preventing the colonization of pathogens. Mounting evidence has suggested gut microbial imbalance (dysbiosis) as a core pathophysiology in the development of GI motility and metabolic disorders, such as irritable bowel syndrome and diabetes. Current research has focused on discovering associations between these disorders and gut microbial dysbiosis; however, whether these associations are a consequence or cause is still mostly unexplored. State-of-the-art studies have investigated how gut microbes communicate with our body systems through microbiota-derived metabolites and how they are able to modulate host physiology. There is now mounting evidence that alterations in the composition of small intestinal microbes have an association with GI dysmotility and metabolic disorders. Although treatment options for gut microbial dysbiosis are currently limited, antibiotics, fecal microbiota transplantation, probiotics, and dietary interventions are currently the best options. However, treatment with broad-spectrum antibiotics has been viewed with skepticism due to the risk of developing antibiotic resistant bacteria. Studies are warranted to elucidate the cellular and molecular pathways underlying gut microbiota-host crosstalk and for the development of a powerful platform for future therapeutic approaches. Here, we review recent literature on gut microbial alterations and/or interactions involved in the pathophysiology of GI dysmotility and metabolic disorders.  
(J Neurogastroenterol Motil 2021;27:19-34)

Key Words  
Diabetes mellitus; Fecal microbiota transplantation; Gastrointestinal microbiome; Irritable bowel syndrome; Metabolic diseases

Received: June 29, 2020 Revised: August 26, 2020 Accepted: October 3, 2020

*Correspondence: Uday C Ghoshal and Seungil Ro are joint corresponding authors.
Uday C Ghoshal, MD, DNB, DM, FACG, RFF  
Department of Gastroenterology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow 226014, India  
Tel: +91-522-2494405, Fax: +91-522-2668017, E-mail: udayghoshal@gmail.com
Seungil Ro, PhD  
Department of Physiology and Cell Biology, University of Nevada School of Medicine, MS 0375, 1664 N Virginia St, Reno, NV 89557, USA  
Tel: +1-775-784-1462, Fax: +1-775-784-6903, E-mail: sro@med.unr.edu
Rajan Singh, Hannah Zogg, and Lai Wei contributed equally as 1st author to this study.
Introduction

Trillions of microorganisms live inside every human being.\textsuperscript{1,2} Not surprisingly, these microbial inhabitants outnumber all of the human cells in the entire body by approximately one order of magnitude (\(10^{14}\) vs \(10^{13}\), respectively).\textsuperscript{3} To better grasp the role that gut microbes play in health and disease, scientists around the globe are investigating gut microbiota and their metabolites that play a fundamental role in modulating metabolic, developmental, and physiological aspects.\textsuperscript{1,4} Many human diseases originate from distorted gut microbiota composition (dysbiosis) leading to dysregulation of physiological and metabolic processes.\textsuperscript{3-5} Gut microbial dysbiosis has been implicated in functional gastrointestinal (GI) disorders including irritable bowel syndrome (IBS), functional dyspepsia (FD), and inflammatory bowel diseases (Crohn’s disease and ulcerative colitis).\textsuperscript{6-9}

In 2019 there were approximately 463 million people suffering from type 2 diabetes (T2D) and 4.2 million deaths due to T2D-related complications.\textsuperscript{10} Currently, T2D is projected to affect 700 million people worldwide by 2045, which could become a greater burden to the medical community already facing grim statistics.\textsuperscript{10} Approximately 50% of diabetic patients also suffer from GI motility disorders including but not limited to diarrhea, fecal incontinence, constipation, dyspepsia, and gastroparesis.\textsuperscript{11-13} GI motility disorders are also extremely common, with approximately 40% of adults suffering from functional bowel disorders worldwide.\textsuperscript{14} There is a great need to understand the molecular mechanisms that occurs in conditions associated with dysbiosis and how these altered pathways contribute to the development of GI motility disorders and T2D. There are currently many studies focused on creating a deeper understanding of microbiota-related mechanisms of disease pathogenesis with hope that it will lead to the development of effective, preventative, and therapeutic interventions.\textsuperscript{15-19} Here, we summarize the impact that the gut microbiome and its metabolites have on both GI motility disorders and metabolic diseases. Although, extensive review of current literature identifies a lack of knowledge, the question persists as to whether the disruption of gut microbial communities is a consequence or cause of chronic GI and metabolic diseases.

Function, Composition, and the Dysbiosis of the Gut Microbiota

The GI tract is home to vast microbial communities including bacteria, fungi, archaea, and viruses.\textsuperscript{1-20} The microbe population is more sparse in the upper gut (stomach, duodenum, and jejunum) with approximately \(10^3\) bacteria per mL of aspirate, where there are approximately \(10^7-10^{12}\) bacteria per mL of aspirate in the lower gut (ileum and proximal colon).\textsuperscript{21} Gut microbiota perform many diverse functions, such as aiding in the digestion of food, production of essential vitamins, synthesis of metabolites, prevention of pathogenic bacteria colonization, gut-immune regulation, drug metabolism, detoxification, and maintenance of GI physiological homeostasis (Fig. 1).\textsuperscript{20,22,23} Hence, maintaining a healthy proportion of beneficial microbes, also called eubiosis, is essential for human health.

Gut microbial imbalance, known as dysbiosis, can include an increase in the proportion of small bowel bacteria, alteration in the relative proportion of benevolent microbes to pathogenic ones, as well as the translocation of colonic bacteria.\textsuperscript{4,24} At a fundamental
level, there are many contributing factors for the progression of a diseased states including microbe-microbe interactions, microbial metabolites, host immune response, host physiology, diet, and the host environment.  

Gut microbiota composition and relative abundance changes throughout the varying microenvironments of the GI tract and over 50 bacterial phyla have been identified in the human GI tract so far. In the healthy host, Bacteroidetes and Firmicutes are the most predominantly found phyla in the gut, while Proteobacteria, Verrucomicrobia, Actinobacteria, Fusobacteria, and Cyanobacteria are found in much smaller proportions. Generally, the various segments of the GI tract are colonized by different microbial communities; Gram-positive bacteria are prevalent in the small intestine, while Gram-negative bacteria are predominant in the large intestine. Approximately 95% of bacteria presiding in the colon are strict anaerobes, which is determined by the available nutrients. Small intestinal bacterial overgrowth (SIBO) is largely determined by intrinsic and extrinsic factors. The most notable intrinsic factors preventing this overgrowth of bacteria are gastric acid and bile acid (BA) secretion, peristaltic movement, normal gut defense mechanisms, the production of mucin, gut antibacterial peptides, and prevention of bacterial retrograde translocation from the lower gut to the upper gut via the ileocecal valve. Extrinsich factors include nutrient intake and diet, bacterial and viral infection, medications altering motility (prokinetics), and drugs modulating the gut microbiota, for instance, pre and probiotics, proton pump inhibitors, H2 blockers, and antibiotics. If any one of the extrinsic factors cause imbalance to off-set the many protective mechanisms set in place, commensal and pathogenic gut microbiota may colonize disproportionately and lead to dysbiosis. One example of dysbiosis is the development of SIBO, diagnosed by overall bacterial overgrowth equal to or greater than 10^3 CFU per mL of upper gut (eg, jejunal) aspirate culture. However, overgrowth of bacteria equal to or greater than 10^3 CFU/mL of upper gut aspirate has also been included in the diagnosis of SIBO recently. Based on jejunal aspirate cultures, one study showed that Escherichia coli, Streptococcus species (spp.), Pseudomonas aeruginosa, Staphylococcus spp., Acinetobacter baumannii, Acinetobacter lwoffii, Enterococcus faecium, Klebsiella pneumoniae, and Enterococcus faecalis were predominantly found in patients with SIBO who suffered altered GI motility.

Gut Microbiota Affect Host Physiology

The gut microbiota provide its host with essential health benefits primarily by maintaining healthy gut homeostasis. Currently, scientists are investigating what makes a healthy gut microbiome, and exploring the molecular mechanisms and signaling pathways that allow for crosstalk between gut microorganisms and the host. Many studies have shown that pathogens have the ability to impair the epithelial barrier function. In contrast, commensal gut microbiota have been found to act as gatekeepers to protect epithelial cell integrity from penetration and disease caused by pathogens. Other beneficial effects of commensal gut microbiota include micronutrient production, such as vitamin K and folate. Colon bacteria ferment unabsorbed carbohydrates to short-chain fatty acids (SCFAs), which can be subsequently absorbed through the colonic mucosa and used as an additional energy source. Most importantly, commensal gut microbiota are essential to prevent colonization and translocation with pathogenic bacteria at the intestinal epithelial barrier.

SIBO has been found to lead to several complications in affected hosts, including destruction of microvilli and heightened epithelial inflammatory response, which often results in impaired absorption. The bacteria responsible for the harmful effects of SIBO are often aerobes; however, in a healthy gut the small intestine primarily houses facultative anaerobes. This microbial shift in patients with SIBO leads to the malabsorption of fat and a deficiency in the fat-soluble vitamins D, E, A, and K. Common symptoms of SIBO are abdominal discomfort, gas, distension, and bloating and are likely caused by the dysregulated fermentation of carbohydrates and bacterial colonization in the small intestine, which produce methane, carbon dioxide, and hydrogen.  

Gut Microbial Dysbiosis in GI Dysmotility and Metabolic Disorders

Gut Microbial Alterations and Gastrointestinal Dysmotility

Peristaltic movements are of paramount importance for food to properly travel through the gut. Peristalsis is generated by a coordination of both contraction and relaxation of the circular and longitudinal smooth muscles of the muscularis externa and are regulated by the enteric nervous system (ENS), GI smooth muscle cells, pacemaker cells called interstitial cells of Cajal, enterochromaffin (EC) cells, as well as other factors. Furthermore, altered microbiota composition of the lumen and mucus layer covering the epithelium.
Facultative aerobes and anaerobes such as *Enterococcus* spp. and *Proteus mirabilis*. Not surprisingly, in patients with SIBO versus those without, the small intestinal luminal contents had different metabolomic profiles, and in another study patients with malabsorption syndrome had higher quantities of total BAs, lactate, acetate, and formate compared to controls. A similar study in subjects with SIBO found that patients were also unable to properly absorb these substances. Additionally, patients with malabsorption syndrome were found to have a positive correlation with the quantity of acetate and the degree of symptom severity of SIBO. In the same study, unconjugated BAs positively correlated with the degree of steatorrhea, or malabsorption of fat in the intestine. This indicates that bacteria commonly found in the small intestine of SIBO patients contributes to the excess production of acetate and deconjugated BA, leading to malabsorption of fat. The inability of intestinal epithelial cells to absorb SCFAs leads to further damage in small intestinal epithelial cells, inducing barrier dysfunction, ileal brake, leading to stasis and eventually bacterial colonization.

**Gut Microbial Alterations and Metabolic Disorders**

There have been many studies demonstrating that gut microbiota contributes to the regulation of metabolic homeostasis and that microbial dysbiosis can lead to metabolic dysregulation and diseases; mechanisms include but are not limited to changes to gut barrier function and metabolic inflammation. Furthermore, there is surmounting evidence of the importance of the microbiota in regulating body weight and in the development of T2D. For example, fecal microbiota transplantation (FMT) with healthy gut bacteria improves insulin sensitivity and weight loss in mice and human subjects. The gut microbiota are able to produce and absorb host metabolism signaling molecules by regulating available energy extracted from indigestible carbohydrates to the host. While the primary phyla of the healthy gut remain relatively stable, colonization can be modified by diet, including prebiotics, and with probiotics and antibiotics, which have an effect on the production of microbial metabolites. Still, future studies are warranted to confirm the occurrence of a gut microbial shift caused by the administration of prebiotics and probiotics. Antibiotics have the ability to decimate microbial populations and have been associated with the development of metabolic disease, especially with early life exposure. Conversely, there has been recent evidence that the use of antibiotics may help regulate metabolic function by improving peripheral insulin sensitivity in obese patients. A considerable amount of experimental data has been produced backing the role of microbiota in metabolic regulation and in the genesis of obesity.
should not be unexpected that several studies have found SIBO as a comorbidity in obese and diabetic patients alike. Further, among individuals with T2D, the presence of SIBO has been associated with delayed gut transit, indicating an association between gut microbial dysbiosis, GI dysmotility, and metabolic disorder. However, present knowledge is lacking robust and highly-controlled human studies examining the effects of microbial mechanisms on host metabolism. As discussed, these studies provide evidence that changes in the gut microbiota may provide an auspicious platform to treat diabetes-related metabolic disorders.

**Microbial Signaling Uncovers Pathogenesis of Gastrointestinal Dysmotility and Metabolic Disease**

Microbial signaling via metabolites or structural components of bacteria are transmitted across the intestinal epithelium to communicate with distant organs. Once these signals are transmitted, they are able to affect organs through subsequent signaling via nerves or hormones. Metabolic signaling from the gut microbiota have the potential to significantly affect the host, influencing health status.

**Immune Signals**

Immune signaling begins with the recognition of microbe-associated molecular patterns, which can include structural components such as lipopolysaccharide, flagellin, and peptidoglycan by pattern-recognition receptors. While there are many different types of pattern-recognition receptors, Toll-like receptors, retinoic acid-inducible gene-I-like receptors, and nucleotide-binding oligomerization domain-like receptors located on epithelial and immune cells are commonly used for host-microbe immune interactions. In addition, the aryl hydrocarbon receptor (AHR), which is a transcription factor important for coordinating cellular responses to external stimuli, is stimulated by the Lactobacilli tryptophan ligand, indole-3-aldehyde. Remarkably, it has been shown that in the dysbiosis-associated conditions, the microbiota fail to generate AHR ligands contributing to the pathogenesis of GI and metabolic disorders, as a recent study showed that AHR functions as a biosensor that connect the environment of the intestinal lumen to programming of the ENS via intestinal motility. The ENS regulates most aspects of gut physiology through intrinsic neural networks, which innervate throughout the GI system and is commonly called the second brain. Distinct neuronal transcriptomes have been identified in various delineations of the GI tract as well as microbiota communities in mice. These transcriptome data led to the discovery that AHR has a defined role in regulating microbe-associated intestinal peristalsis in the surveillance pathway of the ENS. Murine studies have also found that AHR deficiency enhances insulin sensitivity and reduces peroxisome proliferator-activated receptor-α, a key metabolic protein. Thus, modulating AHR signaling independently or though gut microbiota modulation could help to treat conditions commonly associated with impaired gut motility and metabolic diseases. Taken together, the studies reviewed demonstrate that gut microbial dysbiosis alters host immune signals, which is a central pathogenic mechanism for GI dysmotility and metabolic disorders.

**Short-chain Fatty Acids**

Butyrate, propionate, and acetate are the 3 most commonly studied SCFAs and are the major fermentation metabolites generated from gut microbial degradation of dietary fiber and help to provide up to 10% of the total energy required by the host. Butyrate, propionate, and acetate are also important multifunctional signals produced by the gut microbiota and can bind to the G-protein-coupled receptors (GPR43 and GPR41), also known as free fatty acid receptor 2 and 3 (FFAR2 and FFAR3), respectively. SCFAs binding to FFAR3 induces expression of the hormone peptide YY in enteroendocrine L-cells, which has been shown to normalize gut motility allowing for an increase in available energy harvested from food in mice. Binding of SCFAs to FFAR2 and FFAR3 in the epithelial cells of the small intestine and colon activates secretion of glucagon-like peptide-1 by L-cells, substantially impacting overall pancreatic function and insulin release, and hormonal effects regulating appetite. Independently, SCFAs perform a wide range of metabolic functions; propionate and butyrate are able to stimulate expression of intestinal gluconeogenic enzymes, and propionate is able to independently act as a precursor for intestinal gluconeogenesis. All 3 major SCFAs are able to activate FFAR2 in mouse white adipose tissue, suppressing insulin signaling and therefore decreasing fat accumulation and further stimulating energy expenditure in hepatocytes and myocytes.

A study by Reigstad et al demonstrated that gut microbiota derived metabolites in human and mouse trigger tryptophan hydroxylase 1 (Tph1) gene expression and 5-HT production in the colon through stimulation of EC cells via SCFAs. In this study, to explore the association between intestinal microbes, gut contractility, and serotoninergic gene expression, germ-free (GF) or humanized (HM; ex-GF mice colonized with human gut microbiota) mice were used. Findings showed that the microbiota from conventionally raised mice and HM mice had caused a significant increase
in colonic mRNAs of TPH1 compared to the GF mice. These studies demonstrate that GI and metabolic homeostasis rely on SCFA production by the gut microbiota, which play a central role in regulating GI motility and metabolic functions.

Tryptamine

Similar to 5-HT, tryptamine is a monoamine metabolite produced from tryptophan by gut bacteria, particularly Ruminococcus gnavus and Clostridium sporogenes, and is found abundantly in human and rodent stool samples. In a study reported by Bhattarai et al., investigators determined that the role of tryptamine in the GI tract is facilitated by the 5-HT4 receptor that is only found in colonic epithelium. Tryptamine produced by both GF and HM mice were shown to increase movement across the colonic epithelium as well as fluid secretions in colonoids, validating the importance of tryptamine for proper intestinal secretion. Additionally, improved GI motility was seen in GF mice that were colonized with tryptamine-producing engineered Bacteroides thetaiotaomicron microbes. This study demonstrates that bacterial metabolites are able to control different facets of host physiology and could be used for localized treatments for GI disorders associated with constipation.

The aforementioned studies provide evidence that metabolites and byproducts essential to gut microbiome signaling fill a specific niche to maintain proper GI function and metabolic regulation. Further, these findings give insight into gut microbiota and host crosstalk alluding to future potential therapeutic options for GI dysmotility and metabolic disorders.

The Gut-Brain Axis and Gut Microbiota: Gastrointestinal Dysmotility and Metabolic Syndrome

The endocrine and nervous systems are able to conduct and coordinate with absolute synergy in each organ system in the body in order to maintain homeostasis. The processes between the brain and the gut are bi-directional; as the brain modulates gut physiology, the gut is also able to influence brain function. This bi-directional interaction has been demonstrated through the improvement in patients with hepatic encephalopathy after gut-microbiota directed antibiotic treatment. Moreover, animal and human studies have demonstrated how the gut microbiota is able to affect brain function. For example, the study by De Palma et al demonstrated that GF mice have altered hippocampal brain-derived neurotrophic factors (BDNF), dysregulated hypothalamic pituitary stress responses, impaired neurotransmission, diminished tryptophan availability and dysregulated metabolism, further demonstrating a connection between the gut microbiota and the gut-brain axis.

Bi-directional gut-brain interactions serve as important modulators of GI functionality influencing motility, gastric secretions, blood flow, immune activity, and visceral sensations. Brain-to-gut bi-directional signaling can also affect the GI tract through indirect signaling between the gut microbiota and the host. Microbial organisms residing in the GI tract can cause increased intestinal epithelial permeability and modulate the mucosal immune response, leading to changes in host physiology. Some evidences support that communication between the gut microbiota and intestinal epithelial cells occurs through luminal release from neurons, Paneth cells, and EC cells. The perception of gut stimuli and modulation of various gut functions are conducted through the emotional motor system. The emotional motor system is described as complimentary parallel outflow systems, which includes the sympathetic and parasympathetic branches of the autonomic system, and endogenous pain-modulation systems. A bi-directional gut-brain microbiota axis is established through the gut microbiota interactions with gut based effector systems and visceral afferent pathways. Also, current research demonstrates that the host 5-HT is synthesized in the gut via microbial-derived metabolites; these findings add further weight to the concept of a gut microbiota-gut-brain axis and its influence on GI homeostasis.

Connecting the dots between the gut microbiota, brain, and metabolic control of insulin secretion, Perry and colleagues explored a pathway involving the “rest-and-digest” and “feed-and-breed” processes. In this study, rats fed a high-fat diet had greater production and turnover of the SCFA, acetate, compared to normal control diet (NCD) rats. They found that by exposing stomachs of NCD rats with acetate, glucose-stimulated insulin secretion (GSIS) was increased, indicating a relationship between microbiota-derived acetate and insulin secretion. The vagus nerve largely controls parasympathetic activity through motor inputs that are sent to various organs and is able to control heart rate, regulate GI movement, aid in the digestion of food, and enhance insulin secretion. Perry et al. demonstrated this by using parasympathetic blockers, atropine or methylatropine, or surgically severing portions of the vagus nerve connecting the gut, to prevent acetate from increasing GSIS. This indicates that the beneficial effects of acetate-inducing GSIS is controlled through the vagus nerve and parasympathetic nervous system. To elucidate the role of microbiota acetate turnover in this study, Perry et al. performed FMT from NCD or high-fat diet donor rats into recipients on the opposite diet. Results showed that acetate levels and GSIS levels from the donor groups were trans-

Rajan Singh, et al
Journal of Neurogastroenterology and Motility

24
ferred to recipient groups, implying that changes in the microbiota regulate acetate turnover, and therefore GSIS. These powerful findings confirmed the gut microbiota-gut-brain axis influences metabolic homeostasis (Fig. 2).

Strong pre-clinical data highlights that the gut microbiota is important for bi-directional interactions of the gut-brain axis in health and in disease. Therefore, gut microbial dysbiosis has pathophysiological effects on gut-brain bi-directional interactions leading to GI dysmotility and metabolic disorders. An emerging area that should be further explored is how the gut-brain axis is affected by the gut microbiota and their derived metabolites leading to metabolic benefits.

**Gut Microbiota Mediated Immune Dysregulation in Gastrointestinal Dysmotility and Metabolic Disease**

The most important function of the GI tract is to take in food particles, digest these to smaller molecules, absorb nutrients, and excrete the undigested byproducts. The GI tract also harnesses the benefits of commensal microbiota, which play a part in regulating the host metabolism and directing proper immunity. Like proper heart function, the functions of the GI tract, such as gut motility, are necessary for life. Current literature suggests proper gut motility is dependent on the interacting forces between the microbiome and ENS with the help of immune cells, like the tissue-resident muscularis macrophages (MMs). MMs are in close proximity to the myenteric plexus of GI smooth muscle. One study explored the functional role of MMs under normal physiological conditions and homeostatic crosstalk between ENS neurons and MMs. Muller et al showed that MMs are a unvarying subset of CX3CR1+ CD11c+ MHCII+ cells, dependent on the secretion of colony stimulatory factor 1 receptor (CSF-1R), a cytokine receptor. Intraperitoneal injection with a low-dose of anti-CSF-1R antibody specifically depleted 80% of MMs, leaving stromal cells and other GI resident macrophage populations unharmed. By depleting this specific subset of macrophages, gastric emptying was accelerated and colonic emptying was reduced in mice. Furthermore, in vitro experiments demonstrated the homeostatic role of MMs in regulating peristalsis showing signs of deregulated and hyperreactive contractions of the muscularis externa. In addition to the distinctive role of MMs to establish the molecular mechanisms contributing to these effects, researchers analyzed the nonimmune MM transcripts and found novel expression of bone morphogenetic protein 2 (BMP2) that is known to stimulate the BMP receptors I and II (BMPRI and BMPRII). Neuronal and smooth muscle development relies on BMP receptors indicating BMP2 may be a candidate for MM-mediated control of peristalsis. It is well established that the intestinal microbiota possess the ability to instruct mucosal immune cells and therefore influence the composition of the gut microbiota.

**Figure 2.** Intestinal barrier dysfunction as a core pathophysiology of gastrointestinal (GI) dysmotility and metabolic disorder. SCFAs, short-chain fatty acids; ZO, zonula occludens; E-cadherin, epithelial cadherin; EC, enterochromaffin; GLP-1, glucagon-like peptide-1; IL, interleukin; M1, classically activated macrophages; M2, alternatively activated macrophages; TGF-β, transforming growth factor beta; HO-1, heme oxygenase-1; TNF-α, tumor necrosis factor alpha; iNOS, inducible nitric oxide synthase; ICC, interstitial cell of Cajal; SMC, smooth muscle cell; L-cell, enteroendocrine cell.
Gut Microbial Dysbiosis Connects Gastrointestinal Dysmotility With Metabolic Disorders

GI dysmotility is commonly diagnosed in patients with metabolic disorders. Recent evidence has shown that gut microbial dysbiosis and the resulting intestinal barrier dysfunction link these 2 conditions. For example, a recent study showed how duodenal microbial dysbiosis is linked with enteropathy and intestinal barrier dysfunction in the environmental enteric dysfunction (EED) condition. EED is a subclinical syndrome characterized by intestinal villous blunting, reduced absorptive capacity, and increased intestinal inflammation. Furthermore, there have been several metabolic consequences, such as malnutrition and stunting, in patients with EED. However, findings from this study raise additional questions: is environmental enteropathy caused by a form of bacterial overgrowth in the small intestine? If so, how does SIBO alter GI motility? In response to these questions, we reviewed an article published on tropical sprue (TS), a type of malabsorption syndrome that has clinical and histological features similar to EED. This study demonstrated that there was increased intestinal bacterial colonization in patients with TS. Furthermore, there is a vicious cycle of SIBO and small intestinal stasis due to the ileal brake induced by unabsorbed fat passing through the ileum. SIBO also deconjugates BAs, which further caused fat malabsorption and may even change gut motility. Malabsorption of fat induces ileal brake by liberating gut hormones such as peptide YY and neuropeptide. Therefore, oroecal transit time was found to be longer in patients with TS than in controls.
Further evidence supporting intestinal barrier dysfunction as a pathogenic mechanism for metabolic disorders is illuminated by 2 recent studies. One study demonstrated that hyperglycemia drives intestinal barrier dysfunction and increases the risk for enteric infection. In contrast, a second study showed loss of the gut barrier integrity triggers activation of islet-reactive T cells and autoimmune diabetes. While it is currently unclear whether intestinal barrier dysfunction or metabolic disorder comes first, it is clear that there is a direct connection between these 2 conditions. Interestingly, research over the past few decades has indicated that intestinal barrier dysfunction is a major pathophysiological mechanism for the development of GI dysmotility and functional bowel disorders. Further studies provided evidence for this connection by demonstrating that the development of IBS follows acute infective gastroenteritis, a condition known as post-infectious IBS. Taken together, the aforementioned studies indicated that intestinal barrier dysfunction is associated with gut microbial dysbiosis and is likely a key pathophysiological mechanism that links metabolic disorders with GI dysmotility.

Furthermore, we reviewed some proof of concept studies that provide a direct connection between metabolic and GI motility disorders through microbial dysbiosis. Landmark studies have demonstrated that altering the gut microbiota during stages of critical developmental has lasting metabolic consequences. A large retrospective cohort study reported that prescription for antibiotics within the first 2 years of life is associated with the development of early childhood obesity. Also, antibiotic-induced depletion of the gut microbiota has been shown to induce changes in 5-HT biosynthesis and to delay GI motility. Moreover, studies have demonstrated that gut microbial alterations, especially alterations leading to increased abundance of methanogens, leads to the development of slow transit constipation. These state-of-the-art studies clearly indicate that intestinal barrier dysfunction, brought about by gut microbial dysbiosis, is a central pathogenic mechanism for metabolic as well as GI motility disorders.

**Treatment Options for Gut Microbial Dysbiosis**

Current management options for gut microbial dysbiosis include antibiotics, FMT, as well as diet and probiotic interventions (Fig. 3).

**Antibiotics**

Minimally absorbed antibiotics neomycin and rifaximin led to improved colonic motility as evidenced in clinical trials in patients with IBS. In addition, several studies have shown that exposure to a combination of antibiotics for approximately 4-8 weeks in obesity mouse models or high-fat diet fed mice substantially improves metabolic parameters including: increased glucose tolerance, reduction in fat mass, and lowered hepatic steatosis in hepatic and systemic inflammation; these changes are also associated with changes in gut microbiota composition, gut barrier dysfunction, and metabolic endotoxemia. However, we desperately need well-designed human clinical trials to test if the efficacy of these intervention techniques are applicable to humans and may lead to manipulation of the gut microbiota contributing to hampered metabolism and the manifestation of metabolic disorders. The most studied treatment for patients with SIBO is rifaximin, a non-systemic antibiotic. A systematic review and meta-analysis (26 studies) of rifaximin reported that SIBO was improved or resolved in 70.8% of patients. However, systemic antibiotics, such as norfloxacin, have also been reported to also eradicate SIBO. A meta-analysis (10 prospective clinical studies) of non-systemic antibiotics found more normal hydrogen-breath tests in patients with SIBO that had been treated with an antibiotic compared to patients that received a placebo (51.1% vs 9.8%, respectively).

**Fecal Microbiota Transplantation**

FMT is also thought to be beneficial in treating microbial dysbiosis as it could restore “healthy” microbes in diseased patients.
However, whether FMT as a treatment for IBS is a panacea or placebo, is still debatable. A double-blind randomized controlled trial including 165 patients with IBS showed that after FMT, IBS symptom severity significantly improved when compared to a placebo control group, although there were no outstanding changes in the degree of overall dysbiosis. In a recent metaanalysis, data pooled from 5 different randomized controlled trials found no significant improvements in IBS symptoms of patients who received FMT versus placebo. However, larger and more rigorous trials are needed; studies included in this meta-analysis were small and included potential for a high-risk of bias. Interestingly, FMT eliminated SIBO in 71% of patients with chronic intestinal pseudo-obstruction. Another study demonstrated the effect of a lean donor (allogenic) versus own (autologous) FMT to recipients with metabolic syndromes. Changes in blood plasma metabolites, such as gamma-aminobutyric acid, indicate metabolic responses responsible for the observed improved insulin sensitivity in the allogenic FMT group. However, this improvement is dependent on the fact that the patient had decreased fecal microbial diversity at the start of the study. Further, changes in intestinal microbiota composition is associated with the beneficial effects on glucose metabolism seen in patients in the allogenic group and may be predicted from fecal microbiota composition before treatment.

Probiotics

Probiotics, live microorganisms, are believed to have favorable effects on the gut microbiota. However, there have only been a few clinical studies examining this option, and they lack consistency. Recently, a meta-analysis found that improved clearance of SIBO was associated with probiotic use. Probiotics have also been shown to confer health benefits in patients with IBS although the mechanism responsible for improved symptomology has yet to be elucidated. Another study found that probiotics from fermented camel milk significantly restored blood glucose and lipid levels back to healthy levels in the db/db T2D mouse model. In addition, researchers found that insulin secretion was improved in probiotic treated diabetic mice due to upregulation of GPR43/41, which improved glucose-triggered glucagon-like peptide-1 secretion. Taken together, the studies presented show promise for probiotic treatment in GI motility disorders as well as metabolic disease.

Dietary Intervention

“You and your microbiome are what you eat.” Our gut microbiome is largely influenced by our diet because it modulates the richness of specific colonizers and their individual and collective functions. Microbial community changes facilitated by diet could have a detrimental effect for host health due to the essential role that the microbiome plays in regulating host physiology. A superlative option for a low-risk treatment intended to modulate the microbiome would be to change the patients’ diet. Therefore, utilizing diet and diet-based studies to change microbial communities could present novel therapeutic strategies for conditions in which the gut microbiota and its associated metabolic communities have been shown to harm the host or be key in disease pathogenesis. An exciting question arises of whether the presence of the individual’s specific microbiome fingerprint can actually influence disease pathogenesis. An exciting question arises of whether the presence of the individual’s specific microbiome fingerprint can actually influence dietary preferences of the host, and therefore influencing positive feedback loops. In a study in which patients with obesity were assigned several different control diets, researchers found that the fecal microbiota profiles associated more by individual than by diet. On the contrary, in response to the dietary changes, marked changes were found in the relative abundance of dominant microbial phylotypes. Wu et al reported a correlation between long-term dietary habits and 2 enterotypes that were defined in 96 adults. High fiber intake conferred a “Prevotella-type” community and high protein intake was associated with a “Bacteroides-type” community. This implies that dietary patterns may influence the enterotypes found in the host. Another interesting study found that populations of Italian and African children had significant differences in fecal microbiota, which can be explained due to different dietary habits. In these samples, Italian children had higher intakes of starch and proteins compared to African populations and showed a higher proportion of Bacteroides spp. and Firmicutes, suggesting that both short-term and long-term dietary shifts can lead to compositional changes of the gut microbiota.

Dietary intervention has the potential to be a powerful tool in helping patients overcome microbial dysbiosis. In patients suffering from conditions as a result of gut dysbiosis, translocated colonic bacteria residing in the small bowel ferment carbohydrates causing excessive gas, abdominal pain, and bloating. Therefore, with the temporary restriction of dietary components, such as diets low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAP), hence the FODMAP, has been suggested to improve symptoms of IBS and of dysbiosis. Low FODMAP diets have been associated with reduced absolute abundance of bacteria, which may have significant beneficial effects in the treatment of SIBO or other dysbiosis conditions. Moreover, a diet high in complex carbohydrates preferentially encourages the growth of less pathogenic bacteria than a diet rich in fats or protein. Primarily vegetarian diets abundant in fiber lead to increased production of...
SCFAs, which inhibit potentially invasive bacteria from colonizing the gut. 160 While there is accumulating evidence supporting the role of diet on gut microbial composition, more research is needed to accurately deduce the effect of different diets on the gut microbiota.

Conclusions and Further Directions

Constant communication between the gut microbiota derived metabolites and human body systems regulates physiological aspects of health and disease. Current literature demonstrates that metabolic syndrome is highly influenced by the gut and supports the hypothesis that metabolic disorders may begin there. Metabolic disease is a multi-factorial condition that makes it difficult to unravel a causative effect of the microbiome on the pathogenesis of this condition. Further, gut microbiota mediated immune dysregulation and intestinal barrier dysfunction emerges as a core pathophysiology of GI dysmotility and metabolic disease. However, it should be noted that these disorders are not mutually inclusive; patients may have GI dysmotility without the co-occurrence of metabolic disorders and vice versa.

Evidence has emerged demonstrating a potential position of the gut microbiome in GI dysmotility and metabolic disorders (Fig. 4). A major challenge in studying the gut microbiota is in translating and applying data into physiologically relevant mechanisms. One way to go about facing this challenge is to isolate specific bacterial strains, or analyze how they are affected by specific macronutrients commonly found in humans, and use the information obtained to elucidate biomarkers that may be used to find better treatments for GI dysmotility and metabolic diseases. These biomarkers may also allow for the identification of mechanisms in which the microbial metabolites lead to or prevent the development of disease states. Also, due to obscure small intestinal microbiome research, more attention is needed on the pathogenesis of SIBO in GI dysmotility and metabolic diseases. Using next generation sequencing techniques to explore small intestinal microbiomes, together with better sampling of the small bowel aspirate, may allow us to prevent cases of antibiotic resistance and help better understand the microbial pathogenesis of SIBO.

The collaborative work between microbiologists, gastroenterologists, endocrinologists, and epidemiologists along with improvements in the analysis of microbial markers, microbial metabolites, and molecular signals will lead to thrilling discoveries in the future. The closer we can get to the microbial pathogenesis of the gut microbial alterations and exploring crosstalk with the host, the more effectively we can treat and manage GI dysmotility and related metabolic manifestations. The statement from Hippocrates that “all disease begins in the gut” is becoming progressively more accepted with increasing knowledge of the gut microbiota-gut-brain axis and its influence on human health and disease when altered.

Financial support: None.

Conflicts of interest: None.

Author contributions: Rajan Singh, Hannah Zogg, Lai Wei, and Allison Bartlett reviewed the literature and drafted the original manuscript and figures; and Seungil Ro, Uday C Ghoshal, and Singh Rajender edited the manuscript and provided important intellectual directives.

References

1. Brody H. The gut microbiome. Nature 2020;577:S5.
2. Cani PD. Human gut microbiome: hopes, threats and promises. Gut 2018;67:1716-1725.
3. Prakash S, Rodes L, Coussa-Charley M, Tomaro-Duchesneau C. Gut microbiota: next frontier in understanding human health and development of biotherapeutics. Biologies 2011;6:71-86.
4. Cani PD. Gut microbiota: changes in gut microbes and host metabolism: squaring the circle? Nat Rev Gastroenterol Hepatol 2016;13:563-564.

5. Lynch SV, Pedersen O. The human intestinal microbiome in health and disease. N Engl J Med 2016;375:2369-2379.

6. Pttrayan R, Lau JT, Yuan Y, et al. Gut microbiota in patients with irritable bowel syndrome—a systematic review. Gastroenterology 2019;157:97-108.

7. Barbara G, Feinle-Bisset C, Ghoshal UC, et al. The intestinal microenvironment and functional gastrointestinal disorders. Gastroenterology 2016;150:1305-1318, e8.

8. Ghoshal UC. Marshall and Warren Lecture 2019: a paradigm shift in pathophysiological basis of irritable bowel syndrome and its implication on treatment. J Gastroenterol Hepatol 2020;35:712-721.

9. Pttrayan R, Lau JT, Leontiadis GI, et al. Differences in gut microbiota in patients with vs without inflammatory bowel diseases: a systematic review. Gastroenterology 2020;158:930-946, e1.

10. Cho NH, Shaw JE, Kararanga S, et al. IDF Diabetes Atlas: global estimates of diabetes prevalence for 2017 and projections for 2045. Diabetes Res Clin Pract 2018;138:271-281.

11. Chung RS, Locke GR 3rd, Schleck CD, Zinsmeister AR, Melton LJ 3rd, Talley NJ. Risk of gastroparesis in subjects with type 1 and 2 diabetes in the general population. Am J Gastroenterol 2012;107:82-88.

12. Halland M, Bharucha AE. Relationship between control of glycemia and gastric emptying disturbances in diabetes mellitus. Clin Gastroenterol Hepatol 2016;14:929-936.

13. Camilleri M, Chedid V, Ford AC, et al. Gastroparesis. Nat Rev Dis Primers 2018;4:41.

14. Sperber AD, Bangdiwala SI, Drossman DA, et al. Worldwide prevalence and burden of functional gastrointestinal disorders, results of Rome Foundation Global Study. Gastroenterology Published Online First: 12 Apr 2020. doi: 10.1053/j.gastro.2020.04.014.

15. Öhman L, Törnblom H, Simrén M. Crosstalk at the mucosal border: importance of the gut microenvironment in IBS. Nat Rev Gastroenterol Hepatol 2015;12:36-49.

16. Bhattachar Y, Williams BB, Battaglioni EJ, et al. Gut microbiota-produced tryptamine activates an epithelial g-protein-coupled receptor to increase colonic secretion. Cell Host Microbe 2018;23:775-785, e5.

17. Obuta Y, Castaño Á, Boeing S, et al. Neuronal programming by microbiota in luminal overgrowth of indigenous gut flora. Am J Gastroenterol 2019;104:494-500.

18. Erdogan A, Rao SS, Gulley D, Jacobs C, Lee YY, Badger C. Small intestinal bacterial overgrowth: duodenal aspiration vs glucose breath test. Neurogastroenterol Motil 2015;27:481-489.

19. Peralta S, Cortone C, Dovery T, Almasio PL, Crazia A. Small intestine bacterial overgrowth and irritable bowel syndrome-related symptoms: experience with rifaximin. World J Gastroenterol 2009;15:2628-2631.

20. Ziegler TR, Cole CR. Small bowel bacterial overgrowth in adults: a potential contributor to intestinal failure. Curr Gastroenterol Rep 2007;9:463-467.

21. Ghoshal UC, Goel A, Quigley EMM. Gut microbiota abnormalities, small intestinal bacterial overgrowth, and non-alcoholic fatty liver disease: an emerging paradigm. Indian J Gastroenterol 2020;39:9-21.

22. Ghoshal UC, Baba CS, Ghoshal U, et al. Low-grade small intestinal bacterial overgrowth is common in patients with non-alcoholic steatohepatitis on quantitative jejunal aspirate culture. Indian J Gastroenterol 2017;36:390-399.

23. Eisenstein M. The hunt for a healthy microbiome. Nature 2020;577:S6-S8.
40. Odenwald MA, Turner JR. The intestinal epithelial barrier: a therapeutic target? Nat Rev Gastroenterol Hepatol 2017;14:9-21.
41. Vancamelleke M, Vermeire S. The intestinal barrier: a fundamental role in health and disease. Expert Rev Gastroenterol Hepatol 2017;11:821-834.
42. Lussiart AC, Parkos CA, Nusrat A. Inflammation and the intestinal barrier: leukocyte-epithelial cell interactions, cell junction remodeling, and mucosal repair. Gastroenterology 2016;151:616-632.
43. Köhler H, McCormick BA, Walker WA. Bacterial-enterocyte crosstalk: cellular mechanisms in health and disease. J Pediatr Gastroenterol Nutr 2003;36:175-185.
44. Jørgensen JR, Fitch MD, Mortensen PB, Fleming SE. In vivo absorption of medium-chain fatty acids by the rat colon exceeds that of short-chain fatty acids. Gastroenterology 2001;120:1152-1161.
45. Shindo K, Machida M, Koide K, Fukuma M, Yamazaki R. Deconjugation ability of bacteria isolated from the jejunal fluid of patients with progressive systemic sclerosis and its gastric pH. Hepatogastroenterology 1998;45:1643-1650.
46. Gorbach SL. Probiotics and gastrointestinal health. Am J Gastroenterol 2000;95(1 suppl):S2-S8.
47. Bämmler AJ, Sperandio V. Interactions between the microbiota and pathogenic bacteria in the gut. Nature 2016;535:85-93.
48. Kaufman SS, Loseke CA, Lupo JV, et al. Influence of bacterial overgrowth and intestinal inflammation on duration of parenteral nutrition in children with short bowel syndrome. J Pediatr 1997;131:356-361.
49. Ament ME, Shimoda SS, Saunders DR, Rubin CE. Pathogenesis of steatorrhea in three cases of small intestinal stasis syndrome. Gastroenterology 1972;63:728-747.
50. Riepe SP, Goldstein J, Alpers DH. Effect of secreted Bacteroides proteases on human intestinal brush border hydrolases. J Clin Invest 1980;66:314-322.
51. Giannella RA, Rout WR, Tskes P, Pejov M. Jejunal brush border injury and impaired sugar and amino acid uptake in the blind loop syndrome. Gastroenterology 1974;67:965-974.
52. Sachdev AH, Pimentel M. Gastrointestinal bacterial overgrowth: pathogenesis and clinical significance. Ther Adv Chronic Dis 2013;4:223-231.
53. Dhibase JK, Young RJ, Vanderhoof JA. Enteric microbial flora, bacterial overgrowth, and short-bowel syndrome. Clin Gastroenterol Hepatol 2006;4:11-20.
54. Sanders KM, Koh SD, Ro S, Ward SM. Regulation of gastrointestinal motility—insights from smooth muscle biology. Nat Rev Gastroenterol Hepatol 2012;9:633-645.
55. Sanders KM. Spontaneous electrical activity and rhythmicity in gastrointestinal smooth muscles. Adv Exp Med Biol 2019;1124:3-46.
56. Sanders KM, Kito Y, Hwang SJ, Ward SM. Regulation of gastrointestinal smooth muscle function by intestinal cells. Physiology (Bethesda) 2016;31:316-326.
57. Spencer NJ, Hu H. Enteric nervous system: sensory transduction, neural circuits and gastrointestinal motility. Nat Rev Gastroenterol Hepatol 2020;17:338-351.
58. Spencer NJ, Nicholas SJ, Robinson L, et al. Mechanisms underlying distension-evoked peristalsis in guinea pig distal colon: is there a role for enterochromaffin cells? Am J Physiol Gastrointest Liver Physiol 2011;301:G519-G527.
59. Keating DJ, Spencer NJ. What is the role of endogenous gut serotonin in the control of gastrointestinal motility? Pharmacol Res 2019;140:50-55.
60. Grover M, Farrugia G, Stanghellini V. Gas troprocess: a turning point in understanding and treatment. Gut 2019;68:2238-2250.
61. Dickson I. Microbiota modulate ENS maturation. Nat Rev Gastroenterol Hepatol 2018;15:454-455.
62. Shukla R, Ghoshal U, Dhole TN, Ghoshal UC. Fecal microbiota in patients with irritable bowel syndrome compared with healthy controls using real-time polymerase chain reaction: an evidence of dysbiosis. Dig Dis Sci 2015;60:2953-2962.
63. Malinen E, Runtili T, Kajander K, et al. Analysis of the fecal microbiota of irritable bowel syndrome patients and healthy controls with real-time PCR. Am J Gastroenterol 2005;100:373-382.
64. Tap J, Derrien M, Törnblom H, et al. Identification of an intestinal microbiota signature associated with severity of irritable bowel syndrome. Gastroenterology 2017;152:111-123, e8.
65. Salem AE, Singh R, Ayoub YK, Khairy AM, Mullin GE. The gut microbiome and irritable bowel syndrome: state of art review. Arab J Gastroenterol 2018;19:136-141.
66. Ghoshal UC, Ghoshal U, Das K, Misra A. Utility of hydrogen breath tests in diagnosis of small intestinal bacterial overgrowth in malabsorption syndrome and its relationship with oro-cecal transit time. Indian J Gastroenterol 2006;25:6-10.
67. Ghoshal U, Ghoshal U, Ayagari A, et al. Tropical sprue is associated with contamination of small bowel with aerobic bacteria and reversible prolongation of oroecal transit time. J Gastroenterol Hepatol 2003;18:540-547.
68. Nakamura K, Sakarani N, Takakawa A, Ayale T. Paneth cell alpha-defensins and enteric microbiota in health and disease. Biosci Microbiota Food Health 2016;35:57-67.
69. Simeonova D, Ivanovska M, Murdjeva M, et al. Recognizing the leaky gut as a trans-diagnostic target for neuroimmune disorders using clinical chemistry and molecular immunology assays. Curr Top Med Chem 2018;18:1641-1653.
70. Ghosh D, Porter E, Shen B, et al. Paneth cell trypsin is the processing enzyme for human defensin-5. Nat Immunol 2002;3:583-590.
71. Salzman NH, Ghosh D, Hutten KM, Peterson Y, Bevins CL. Protection against enteric salmonellosis in transgenic mice expressing a human intestinal defensin. Nature 2003;422:522-526.
72. Ghoshal UC, Shukla R, Ghoshal U, et al. The gut microbiota and irritable bowel syndrome: friend or foe? Int J Inflamm 2012;2012:151085.
73. Pimentel M, Kong Y, Park S. IBS subjects with methane on lactulose breath test have lower postprandial serotonin levels than subjects with hydrogen. Dig Dis Sci 2004;49:84-47.
74. Mackie RI, Şahr I, Gaskins HR. Developmental microbial ecology of the neonatal gastrointestinal tract. Am J Clin Nutr 1999;69:1035S-1045S.
the upper gut in patients with small intestinal bacterial overgrowth syndrome. Am J Gastroenterol 1999;94:1327-1331.
76. Sachdev AH, Hament M. Antibiotics for irritable bowel syndrome: rationale and current evidence. Curr Gastroenterol Rep 2012;14:439-445.
77. Posserud I, Stotzer PO, Björnsson ES, Abrahamsson H, Simrén M. Small intestinal bacterial overgrowth in patients with irritable bowel syndrome. Gut 2007;56:802-808.
78. Bala L, Ghoshal UC, Ghoshal U, et al. Malabsorption syndrome with and without small intestinal bacterial overgrowth: a study on upper-gut aspirate using 1H NMR spectroscopy. Magn Reson Med 2006;56:738-744.
79. Gilbert JA, Blaser MJ, Caporaso JG, Jansson JK, Lynch SV, Knight R. Current understanding of the human microbiome. Nat Med 2018;24:392-400.
80. Nicholson JK, Holmes E, Kinross J, et al. Host-gut microbiota metabolic interactions. Science 2012;336:1262-1267.
81. Kootte RS, Levin E, Salójärvi J, et al. Improvement of insulin sensitivity after lean donor feces in metabolic syndrome is driven by baseline intestinal microbiota composition. Cell Metab 2017;26:611-619, e6.
82. Muscogiuri G, Balercia G, Barrea L, et al. Gut: a key player in the pathogenesis of type 2 diabetes? Crit Rev Food Sci Nutr 2018;58:1294-1309.
83. Bouter KE, van Raalte DH, Groen AK, Nieuwdorp M. Role of the gut microbiome in the pathogenesis of obesity and obesity-related metabolic dysfunction. Gastroenterology 2017;152:1671-1678.
84. Johnson AM, Olefsky JM. The origins and drivers of insulin resistance. Cell 2013;152:673-684.
85. Roland BC, Lee D, Miller LS, et al. Obesity increases the risk of small intestinal bacterial overgrowth (SIBO). Neurogastroenterol Motil 2018;30.
86. Sonnenburg JL, Bäckhed F. Diet-microbiota interactions as moderators of human metabolism. Nature 2016;535:56-64.
87. Tremaroli V, Bäckhed F. Functional interactions between the gut microbiota and host metabolism. Nature 2012;489:242-249.
88. Adamska A, Nowak M, Błaciński S, et al. Small intestinal bacterial overgrowth in adult patients with type 1 diabetes: its prevalence and relationship with metabolic control and the presence of chronic complications of the disease. Pol Arch Med Wewn 2016;126:628-634.
89. Rana SV, Malik A, Bhadada SK, Sachdeva N, Morya RK, Sharma G. Malabsorption, orooccal transit time and small intestinal bacterial overgrowth in type 2 diabetic patients: a connection. Indian J Clin Biochem 2017;32:84-89.
90. Sekirov I, Russell SL, Arantes LC, Finlay BB. Gut microbiota in health and disease. Physiol Rev 2010;90:859-904.
91. Medzhitov R. Recognition of microorganisms and activation of the immune response. Nature 2007;449:819-826.
92. Zelante T, Iannitti RG, Cunha C, et al. Tryptophan catabolites from microbiota engage aryl hydrocarbon receptor and balance mucosal reactivity via interleukin-22. Immunity 2013;39:372-385.
93. Xu CX, Wang C, Zhang ZM, et al. Aryl hydrocarbon receptor deficiency protects mice from diet-induced adiposity and metabolic disorders through increased energy expenditure. Int J Obes (Lond) 2015;39:1300-1309.
94. Bock KW. Aryl hydrocarbon receptor (AHR) functions in NAD(+) metabolism, myelopoiesis and obesity. Biochem Pharmacol 2019;163:128-132.
95. Wang C, Xu CX, Krager SL, Bottum KM, Liao DF, Tischkau SA. Aryl hydrocarbon receptor deficiency enhances insulin sensitivity and reduces PPAR-alpha pathway activity in mice. Environ Health Perspect 2011;119:1739-1744.
96. Bergman EN. Energy contributions of volatile fatty acids from the gastrointestinal tract in various species. Physiol Rev 1990;70:567-590.
97. Samuel BS, Shaito A, Motoike T, et al. Effects of the gut microbiota on host adiposity are modulated by the short-chain fatty-acid binding G protein-coupled receptor, Gpr41. Proc Natl Acad Sci USA 2008;103:16767-16772.
98. Tölstort G, Heffron H, Lam YS, et al. Short-chain fatty acids stimulate glucagon-like peptide-1 secretion via the G-protein-coupled receptor FFA2. Diabetes 2012;61:364-371.
99. Fava S. Glucagon-like peptide 1 and the cardiovascular system. Curr Diabetes Rev 2014;10:302-310.
100. De Valder F, Kovatcheva-Datchary P, Goncalves D, et al. Microbiota-generated metabolites promote metabolic benefits via gut-brain neural circuits. Cell 2014;156:84-96.
101. Kimura I, Ozawa K, Inoue D, et al. The gut microbiota suppresses insulin-mediated fat accumulation via the short-chain fatty acid receptor GPR43. Nat Commun 2013;4:1829.
102. Reigstad CS, Salmonson CE, Rainey JF 3rd, et al. Gut microbes promote colonic serotonin production through an effect of short-chain fatty acids on enterochromaffin cells. FASEB J 2015;29:1395-1403.
103. Williams BB, Van Benschoten AH, Cimernancic P, et al. Discovery and characterization of gut microbiota decarboxylases that can produce the neurotransmitter tryptamine. Cell Host Microbe 2014;16:495-503.
104. Ghoshal UC. Gut microbiota-brain axis modulation by a healthier microbiological microenvironment: facts and fictions. J Neurogastroenterol Motil 2018;24:4-6.
105. Quigley EMM. Microbiota-brain-gut axis and neurodegenerative diseases. Curr Neurol Neurosci Rep 2017;17:94.
106. Garrovich M, Zocco MA, Roccarrina D, Ponzianni FR, Gasbarrini A. Prevention and treatment of hepatic encephalopathy: focusing on gut microbiota. World J Gastroenterol 2012;18:6693-700.
107. De Palma G, Collins SM, Bercik P. The microbiota-gut-brain axis in functional gastrointestinal disorders. Gut Microbes 2014;5:419-429.
108. Rheer SH, Pithoulakis C, Mayer EA. Principles and clinical implications of the brain-gut-enteric microbiota axis. Nat Rev Gastroenterol Hepatol 2009;6:306-314.
109. Shanky KA, Beck PL, McKay DM. Neuroimmunophysiology of the gut: advances and emerging concepts focusing on the epithelium. Nat Rev Gastroenterol Hepatol 2018;15:765-784.
110. Saltzman NH, Underwood MA, Bevins CL. Paneth cells, defensins, and the commensal microbiota: a hypothesis on intimate interplay at the intestinal mucosa. Semin Immunol 2007;19:70-83.
111. Fung TC, Vuong HE, Luna CDG, et al. Intestinal serotonin and fluorine exposure modulate bacterial colonization in the gut. Nat Microbiol...
112. Clemente JC, Ursell LK, Parfrey LW, Knight R. The impact of the gut microbiota on human health: an integrative view. Cell 2012;148:1258-1270.

113. Robinette ML, Colonna M. GI motility: microbiota and macrophages join forces. Cell 2014;158:239-240.

114. Mikkelsen HB. Intestinal cells of cajal, macrophages and mast cells in the gut musculature: morphology, distribution, spatial and possible functional interactions. J Cell Mol Med 2010;14:818-832.

115. Muller PA, Kocsó B, Rajani GM, et al. Crosstalk between muscularis macrophages and enteric neurons regulates gastrointestinal motility. Cell 2014;158:300-313.

116. Olofsson PS, Rosas-Ballina M, Levine YA, Tracey K. Rethinking inflammation: neural circuits in the regulation of immunity. ImmunoL Rev 2012;248:188-204.

117. Parkhurst CN, Yang G, Ninan I, et al. Microglia promote learning-dependent synapse formation through brain-derived neurotrophic factor. Cell 2013;155:1396-1409.

118. Winer DA, Luck H, Tsai S, Winer S. The intestinal immune system in obesity and insulin resistance. Cell Metab 2016;23:413-426.

119. Olefsky JM, Glass CK. Macrophages, inflammation, and insulin resistance. Annu Rev Physiol 2010;72:219-246.

120. Lumeng CN, Bodzin JL, Saltiel AR. Obesity induces a phenotypic switch in adipose tissue macrophage polarization. J Clin Invest 2007;117:175-184.

121. Brestoff JR, Kim BS, Saez SA, et al. Group 2 innate lymphoid cells promote beiging of white adipose tissue and limit obesity. Nature 2015;519:242-246.

122. Gardiou L, Pomé C, Klopp P, et al. The gut microbiota regulates intestinal CD4 T cells expressing RORγt and controls metabolic disease. Cell Metab 2015;22:100-112.

123. Cani PD, Bibiloni R, Knauf C, et al. Changes in gut microbiota control metabolic endotoxemia-induced inflammation in high-fat diet-induced obesity and diabetes in mice. Diabetes 2008;57:1470-1481.

124. Thaiss CA, Levy M, Grosheva I, et al. Hyperglycemia drives intestinal barrier dysfunction and risk for enteric infection. Science 2018;359:1376-1383.

125. Chen KY, Kung VL, Das S, et al. Duodenal microbiota in stunted undernourished children with enteropathy. N Engl J Med 2020;383:321-333.

126. Gehrig JL, Venkatase S, Chang HW, et al. Effects of microbiota-direct ed foods in gnotobiotic animals and undernourished children. Science 2019;365:eaau4732.

127. Ghoshal UC, Srivastava D, Verma A, Ghoshal U. Tropical sprue in 2014: the new face of an old disease. Curr Gastroenterol Rep 2014;16:391.

128. Sorini C, Cosorich I, Lo Conte M, et al. Loss of gut barrier integrity triggers activation of islet-reactive T cells and autoimmune diabetes. Proc Natl Acad Sci USA 2019;116:15140-15149.

129. Camilleri M. Leaky gut: mechanisms, measurement and clinical implications in humans. Gut 2019;68:1516-1526.

130. Barbara G, Grover M, Bercik P, et al. Rome foundation working team report on post-infection irritable bowel syndrome. Gastroenterology 2019;156:46-58, e7.

131. Jess T. Microbiota, antibiotics, and obesity. N Engl J Med 2014;371:2526-2528.

132. Cox LM, Yamanishi S, Sohn J, et al. Altering the intestinal microbiota during a critical developmental window has lasting metabolic consequences. Cell 2014;158:705-721.

133. Scott FI, Horton DB, Mamtani R, et al. Administration of antibiotics to children before age 2 years increases risk for childhood obesity. Gastroenterology 2016;151:120-129, e5.

134. Yano JM, Yu K, Dorakston GP, et al. Indigenous bacteria from the gut microbiota regulate host serotonin biosynthesis. Cell 2015;161:264-276.

135. Shah A, Morrison M, Holtmann G. A novel treatment for patients with constipation: dawn of a new age for translational microbiomeresearch? Indian J Gastroenterol 2018;37:388-391.

136. Low K, Hwang L, Hua J, Zhu A, Morales W, Pimentel M. A combination of rifaximin and neomycin is most effective in treating irritable bowel syndrome patients with methane on lactulose breath test. J Clin Gastroenterol 2010;44:547-550.

137. Ghoshal UC, Srivastava D, Misra A. A randomized double-blind placebo-controlled trial showing rifaximin to improve constipation by reducing methane production and accelerating colon transit: a pilot study. Indian J Gastroenterol 2018;37:416-423.

138. Reijnders D, Goossens GH, Hermes GD, et al. Effects of gut microbiota manipulation by antibiotics on host metabolism in obese humans: a randomized double-blind placebo-controlled trial. Cell Metab 2016;24:63-74.

139. Rao SSC, Bhagvatwala J. Small intestinal bacterial overgrowth: clinical features and therapeutic management. Clin Transl Gastroenterol 2019;10:e00078.

140. Gatta L, Scarpignato C. Systematic review with meta-analysis: rifaximin is effective and safe for the treatment of small intestine bacterial overgrowth. Aliment Pharmacol Ther 2017;45:604-616.

141. Shah SC, Day LW, Somsook M, Sewell JL. Meta-analysis: antibiotic therapy for small intestinal bacterial overgrowth. Aliment Pharmacol Ther 2013;38:925-934.

142. Khoruts A, Sadowsky MJ. Understanding the mechanisms of faecal microbiota transplantation. Nat Rev Gastroenterol Hepatol 2016;13:508-516.

143. El-Salhy M, Havelock JK, Gilja OH, Kristoffersen AB, Haasen T. Efficacy of faecal microbiota transplantation for patients with irritable bowel syndrome in a randomised, double-blind, placebo-controlled study. Gut 2020;69:859-867.

144. Ianigo G, Eusebi LH, Black CJ, Gasbarrini A, Cammarota G, Ford AC. Systematic review with meta-analysis: efficacy of faecal microbiota transplantation for the treatment of irritable bowel syndrome. Aliment Pharmacol Ther 2019;50:240-248.

145. Xu D, Chen VL, Steiner CA, et al. Efficacy of fecal microbiota transplantation in irritable bowel syndrome: a systematic review and meta-analysis. Am J Gastroenterol 2019;114:1043-1050.

146. Park JH. Clinical usefulness of fecal microbiota transplantation. J Neurogastroenterol Motil 2017;23:149-150.
147. Vrieze A, Van Nood E, Holleman F, et al. Transfer of intestinal microbiota from lean donors increases insulin sensitivity in individuals with metabolic syndrome. Gastroenterology 2012;143:913-916, e7.
148. Hemarajata P, Versalovic J. Effects of probiotics on gut microbiota: mechanisms of intestinal immunomodulation and neuromodulation. Therap Adv Gastroenterol 2013;6:39-51.
149. Zhong C, Qu C, Wang B, Liang S, Zeng B. Probiotics for preventing and treating small intestinal bacterial overgrowth: a meta-analysis and systematic review of current evidence. J Clin Gastroenterol 2017;51:300-311.
150. Eack P, Aziz Q, Barbara G, et al. Irritable bowel syndrome. Nat Rev Dis Primers 2016;2:16014.
151. Wang Y, Dilibadi D, Wu Y, Sailike J, Sun X, Nabi XH. Composite probiotics alleviate type 2 diabetes by regulating intestinal microbiota and inducing GLP-1 secretion in db/db mice. Biomed Pharmacother 2020;125:109914.
152. Zmora N, Suez J, Elinav E. You are what you eat: diet, health and the gut microbiota. Nat Rev Gastroenterol Hepatol 2019;16:35-56.
153. Pulipati P, Sarkar P, Jakampudi A, et al. The Indian gut microbiota-is it unique? Indian J Gastroenterol 2020;39:133-140.
154. Delzenne NM, Bindels LB. Food for thought about manipulating gut bacteria. Nature 2020;577:32-34.
155. Walker AW, Ince J, Duncan SH, et al. Dominant and diet-responsive groups of bacteria within the human colonic microbiota. ISME J 2011;5:220-230.
156. Wu GD, Chen J, Hoffmann C, et al. Linking long-term dietary patterns with gut microbial enterotypes. Science 2011;334:105-108.
157. De Filippo C, Cavaliere D, Di Paola M, et al. Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa. Proc Natl Acad Sci USA 2010;107:14691-14696.
158. Mehtab W, Agarwal A, Singh N, Malhotra A, Makharia G. All that a physician should know about FODMAPs. Indian J Gastroenterol 2019;38:378-390.
159. Altobelli E, Del Negro V, Angeletti PM, Letella G. Low-FODMAP diet improves irritable bowel syndrome symptoms: a meta-analysis. Nutrients 2017;9:940.
160. Томова А, Буковский И, Ремберт Е, et al. The effects of vegetarian and vegan diets on gut microbiota. Front Nutr 2019;6:47.