Good or bad: gut bacteria in human health and diseases

Hao Wang, Chuan-Xian Wei, Lu Min and Ling-Yun Zhu

ABSTRACT
The human gastrointestinal tract is estimated to be colonised by over $10^{14}$ bacteria, approximately 10-fold of the total number of cells in the human body [1]. Disruptions to the microbiome have been associated with severe pathologies of the host, including metabolic disease, cancer and inflammatory bowel disease [2–4]. Recent studies based on 16 s ribosomal-RNA gene sequencing and metagenomic analysis have started to explore the species diversity of the intestinal microbiome within and between the individuals [5–8]. Among about 1000 bacterial species colonised in human guts, the dominant genera include Bacteroides, Clostridium, Fusobacterium, Eubacterium, Ruminococcus, Peptococcus, Peptostreptococcus and Bifidobacterium [9]. Other genera, like Escherichia and Lactobacillus, are also present in the gut but to a lower degree. There are still many species that have not been identified, because many of them cannot be cultured in vitro.

The composition of the gut microbiota is determined and influenced by a number of endogenous and exogenous factors, such as geographic origin, age, genetics, diet and the use of prebiotics and antibiotics. For instance, antibiotics would disturb the gut microbiota either in septic patients or in a murine model, leading to the alteration of the immune system [10,11]. Yatsunenko et al. compared the bacterial species of faecal samples from individuals of different geographic origins (three populations from the United States and Malawi) and different ages (0–70 years) [12]. Their study shows that the diversity of the gut microbiota within individuals is much higher in adults than in children, but that the inter-individual differences are significantly higher in children than in adults. The composition of the bacterial community shifts to the adult-like pattern within the first three years after birth. Dietary components can also shape the bacterial composition [13]. For example, the Bacteroides genus is highly associated with the consumption of animal proteins, amino acids and saturated fats, which are typical components of Western diet, while the Prevotella genus is associated with the consumption of carbohydrates and simple sugars, which are typical of agrarian societies [13,14]. People with a Bacteroides-dominated gut microbiome will gain a Prevotella-dominated microbiome by switching from a Western diet to a carbohydrates-based diet for an extended period of time. Another study reported that the European microbiome was dominated by taxa typical of the Bacteroides, whereas the African microbiome was dominated by the Prevotella [15]. It has also been shown that the consumption of non-caloric artificial sweeteners, which are widely used as common food additives, can change gut microbiota composition [16].

CONTACT Ling-Yun Zhu lingyunzhu@nudt.edu.cn
* These authors contributed equally to this work.
Gut bacteria and health

Accumulating evidence suggests that gut bacteria play critical roles in maintaining human health in many aspects. For example, gut bacteria could train the immune system, prevent the growth of pathogenic bacteria, regulate the gut development, maintain epithelial integrity, and shape the neuronal development [17–19].

It has been proposed that gut bacteria are required to maintain epithelial integrity by regulating tight junction permeability. *Lactobacillus plantarum*, for example, was reported to regulate tight-junction proteins to protect against chemical-induced disruption of the epithelial barrier [20]. Loss of gut epithelial integrity will allow gut bacteria, bacterial toxins, incompletely digested fats and proteins, and wastes to pass the epithelium into the blood stream, triggering inflammatory responses and leading to gastrointestinal problems, such as abdominal bloating, excessive gas and cramps, and food sensitivities. These symptoms are characteristic of leaky gut syndrome, which exhibits intestinal hyperpermeability. A recent study in mice has identified commensal bacteria-derived short chain fatty acids (SCFAs) as modulators of the epithelial barrier function [21]. SCFAs derived from bacterial metabolism, particularly butyrate, stimulate consumption of intracellular oxygen to form a hypoxia state in the colon, resulting in stabilisation of the transcription factor HIF-1 and increase of epithelial integrity.

It is known that colonising gut bacteria are critical to the normal development of host defense [22]. Germ-free mice have low immunoglobulin concentrations; lymphopenia of lymphoid structures; reduced bone marrow leukocyte pools; and aberrant innate and adaptive immune functions [23]. Strikingly, fully functional development of the GALT (gut-associated lymphatic tissue), a sophisticated set of immune tissues, critically depends on the interactions with an intact bacterial gut flora. In germ-free animals, the GALT cannot fully develop into mature tissue, with no Peyer’s patches and only sparse lymphoid infiltrations [24]. By transiently colonising pregnant female mice, the maternal microbiota shapes the immune system of the offspring [23]. Consequently, the immune system, both innate as well as adaptive, and the commensal microbiota share a mutual and interactive evolution. Specifically, the immune system has a major role in containing the microbiota safely within their gut lumen, and conversely, the microbiota signals essentially to govern the development and functional integrity of the immune system [24]. Using animal models, two studies have shown that metabolites derived from gut bacteria, including butyrate, can induce the differentiation of peripheral regulatory T-cells to adjust the balance between pro- and anti-inflammatory responses [25,26]. Moreover, commensal bacteria in the colon can prevent the invasion of pathogenic bacteria either by competing for nutrients and living space on the mucosal surface, or by producing toxic metabolites, such as bacteriocins, acids and phenols, to inhibit pathogenic bacteria growth [9,27].

Gut bacteria benefit the host in a number of other ways, including regulating gut motility, producing vitamins and controlling the maturation and function of the microglia in the central nervous system (CNS) [28,29]. The gut microbiota is essential for normal CNS development. Generally, the absence of gut microbiota is associated with several CNS developmental problems [30]. Heitz et al. [19] reported that compared with conventionally-raised mice, germ-free animals had an increased expression of PSD-95, and synaptophysin in the striate nucleus changed the microglia properties. Moreover, colonisation with a complex microbiota partially restores microglia features, highlighting the role of gut microbiota in conditioning normal CNS development [31]. Long-range interactions between the gut microbiota and the brain underlie the ability of microbe-based therapies to treat symptoms of multiple sclerosis and depression in mice, and the reported efficacy of probiotics in treating emotional symptoms of chronic fatigue syndrome and psychological distress in humans [32]. Recent studies suggest that the gut microbiota influences CNS development and function, and that gut dysbiosis is associated with significant neurological problems. However, most of these results have been collected in experimental animals and cannot be transferred to humans immediately [31]. In summary, commensal bacteria play numerous important roles in maintaining human health, and they also affect a variety of complex behaviours, including social, emotional and anxiety-like behaviours, and contribute to brain development and function.

Gut bacteria and diseases

Increasing evidence suggests that gut microbiota dysbiosis would lead to a number of diseases, including gastrointestinal disorders [2,33–35], obesity [36–38], cardiovascular diseases [39–41], allergy [42–44] and CNS-related diseases [30,45], which affect a large population in the world. Besides, mood and behaviour are also susceptible to alterations in the gut microbiota [3]. Experimental and clinical trials for treatment of these diseases based on modulating gut bacteria composition have shown promises as a therapeutic strategy of gut microbiota on human diseases.

Inflammatory bowel disease (IBD) is a group of inflammatory conditions in the digestive tract, affecting about 3 million people in the United States [46]. Two major
types of IBD are ulcerative colitis (UC) and Crohn’s disease (CD), both of which have been shown to be associated with dysbiosis of the gut microbiota [47]. By comparing the predominant microbiota from 127 UC patients and 87 age and sex-matched controls, studies have shown that the abundance of two bacterial species, *Roseburia hominis* and *Raecalibacterium prausnitzii*, is significantly lower in UC patients than in controls [48]. Another twin study showed that UC patients have a different gene expression profile (e.g. genes related to oxidative and immune responses) in the colon mucosa compared to their healthy twin siblings, suggesting that such differences are due to the dysbiotic microbiota in UC patients [49]. The dysbiosis in CD patients has been better characterized [50]. One study has identified five dysbiotic bacterial species by comparing the predominant microbiota in CD patients and their relatives [51]. Recent clinical studies based on faecal microbiota transplantation (FMT) for treatment of UC demonstrated that FMT could alter the composition greatly, and a microbiota composition highly similar to that of the donor is reconstituted in the patients with successful treatment. No severe adverse or side effects occur during the treatments and follow-ups [52].

Obesity is tightly associated with specific diets and life styles, both of which can influence the composition of the gut microbiota. Thus, an association between changes in the gut microbiota and the development of obesity has been proposed. An epidemiological study shows that yogurt consumption can prevent age-associated gain of weight, which may be due to the effects of probiotics in the yogurt [53]. Transplanting human faecal microbiota from obese and lean twins to germ-free mice provided direct evidence that the gut microbiota modulates host metabolism to regulate body weight. The mice that received faecal microbiota from the obese twins had increased total and fat mass and showed obesity-associated metabolic phenotypes, something not observed in the mice receiving faecal microbiota from the lean twins [54]. In addition, changes in the gut bacteria contribute to both type-1 diabetes (T1D) and type-2 diabetes (T2D). T1D is an autoimmune disease that results from the destruction of insulin-producing pancreatic beta-cells. One study, using the non-obese diabetic (NOD) mouse model, shows that germ-free NOD mice lacking MyD88 (an adaptor for innate immune receptors that recognise microbial stimuli) develop robust T1D, whereas associating these mice with a defined microbial community attenuates T1D development [55]. T2D is a metabolic disease that results from obesity-linked insulin resistance. Dysbiosis of gut microbiota has also been observed in T2D patients, but the cellular and molecular mechanisms leading to these phenotypes need to be further characterized [56].

Moreover, it has been demonstrated that bidirectional communication between the gastrointestinal tract and the CNS occurs continuously through several routes (including hormonal, immune and neuronal pathways) that are mostly conditioned by the microbiota composition, which has led to the emergence of the ‘microbiota–gut–brain axis’ concept. Altered microbiota composition in the intestines could promote a stage of chronic inflammation that might exacerbate CNS inflammatory diseases, such as multiple sclerosis [57–64].

More and more evidence shows that changes in the composition and diversity of the gut microbiota have a substantial influence on the pathology of CNS disorders, and consequently there has been a growing attention to microbiota-based therapeutics, including probiotics, prebiotics and faecal microbiota transplants [65]. For example, recent studies demonstrate treatment with *Bacteroides fragilis* corrects levels of tight junction proteins and cytokines in mice neurological symptoms related to autism spectrum disorder (ASD) [66–68]. More recently, Liang et al. [69] reported that *Lactobacillus helveticus* NS8 supplementation could greatly improve the behavioural, cognitive, and biochemical aberrations caused by chronic restraint stress, both in rats and children. Together, these studies confirm and demonstrate the hypothesis that probiotic supplementation may be an effective and safe therapy for brain and behaviour disorders.

**Perspectives**

The human gut microbiota may be viewed upon as an organ [70], and contributes to the digestion of food and the breakdown of toxins and drugs, regulates lipid and glucose metabolism, plays a fundamental role in the induction, training and function of the host immune system, modulates gene expression, and reduces inflammation [70]. In addition, 20%–40% of the small molecules in the peripheral blood are microbial metabolites, many of which have profound effects on CNS development and function [31]. Although there are numerous diseases that have been linked to dysbiosis of gut bacteria, it is critical for future studies to distinguish whether dysbiosis is the cause or the result of these diseases, as it determines how intervention strategies would develop. Prebiotics and probiotics have been widely used to treat some diseases, and they have shown great benefits to human health. In some cases, the change of a single bacterial species plays a key role on disease development, while in other cases dysbiosis of multiple species
(microbiota composition) underlies the diseases. In addition, there also could be a potential method for curing patients with their own healthy microbiota preserved in the youth. Thus, future studies should put efforts not only on the exploration of effects from individual bacteria (like mono-association studies), but also on the accurate quantitative analysis of each species in one bacterial community [71].

There is no doubt that the gut microbiota would affect the immune system of the host, and impact the host health and disease subsequently. Emerging evidence has shown that early microbiota colonisation may influence the occurrence of diseases (microbial programming) later [72]. It is not difficult to imagine that each disease could have a unique pattern of gut microbiota. Accordingly, the gut microbiota could be potent biomarkers for disease diagnosis. It is now clear that the interindividual diversity in microbiota composition plays an important role in determining the susceptibility to a wide variety of diseases [73]. However, identifying the precise changes in microbiota composition that play causal roles has remained a largely unrealised goal [73].

Not only do the diverse gut bacteria play a crucial role in the host health, but also the products of gut microbiota, containing proteins, small molecular chemicals and even DNAs could involve in a lot of events, e.g. the gut microbiota provides unique contributions to the diversity of bile acids in the bile acid pool [74,75]. Based on all these features, the gut microbiota may secrete various molecular signatures labelling different diseases. Meanwhile, identification of gut bacteria-derived molecules would greatly facilitate the treatment of these diseases.

Moreover, the host health consists of two aspects: the physiological health and the psychological health. Recently, numerous findings have supported that the gut microbiota participates in almost all of the host health issues, whereas the relationship between the gut bacteria and the psychological conditions is still limited. Thus, more attention should be paid on this area. For instance, children with ASDs who have gastrointestinal conditions, including both physiological and psychological diseases. Identification of microbiota composition and gut bacteria-derived molecules, as well as introducing novel methods for reconstituting the normal gut microbiota composition would greatly facilitate treatments of these diseases, among which preserving one’s own healthy microbiota in the youth for disease treatment in the future should be a promising strategy.

Disclosure statement
No potential conflict of interest was reported by the authors.

Funding
This work was supported by the National Natural Science Foundation of China under [grant number 31500 686] and [grant number 31100 609]; the National University of Defense Technology project under [grant number JC14–02-09] and [grant number ZK16–03-13].

ORCID
Chuan-Xian Wei http://orcid.org/0000-0001-6349-5053
Lu Min http://orcid.org/0000-0003-4954-153X
Ling-Yun Zhu http://orcid.org/0000-0002-0420-4508

References

[1] Zhang YJ, Li S, Gan RY, et al. Impacts of gut bacteria on human health and diseases. Int J Mol Sci. 2015;16(4):7493–7519.
[2] Constante M, Fragoso G, Lupien-Meilleur J, et al. Iron supplements modulate colon microbiota composition and potentiate the protective effects of probiotics in dextran sodium sulfate-induced colitis. Inflamm Bowel Dis. 2017;23(5):753–766.
[3] Postler TS, Ghosh S. Understanding the holobiont: how microbial metabolites affect human health and shape the immune system. Cell Metab. 2017;26(1):110–130.
[4] Norman, JM, Handley SA, Baldridge MT, et al. Disease-specific alterations in the enteric virome in inflammatory bowel disease. Cell. 2015;160(3):447–460.
[5] Gill SR, Pop M, Deboy RT, et al. Metagenomic analysis of the human distal gut microbiome. Science. 2006;312(5778):1355–1359.
[6] Lay C, Rigottier-Gois L, Holmstrom K, et al. Colonial microbiota signatures across five northern European countries. Appl Environ Microbiol. 2005;71(7):4153–4155.
[7] Hayashi H, Sakamoto M, Benyo N. Phylogenetic analysis of the human gut microbiota using 16S rDNA clone libraries and strictly anaerobic culture-based methods. Microbiol Immunol. 2002;46(8):535–548.
[8] Eckburg PB, Bik EM, Bernstein CN, et al. Diversity of the human intestinal microbial flora. Science. 2005;308(5728):1635–1638.
[9] Guarner F, Malagelada JR. Gut flora in health and disease. Lancet. 2003;361(9356):512–519.
[10] Strzepa A, Majewska-Szczeniak M, Lobo FM, et al. Broad spectrum antibiotic enrofloxacin modulates contact sensitivity through gut microbiota in a murine model. J Allergy Clin Immunol. 2017;140(1):121–133.

[11] Lankelma JM, van Vught LA, Belzer C, et al. Critically ill patients demonstrate large interpersonal variation in intestinal microbiota dysregulation: a pilot study. Intensive Care Med. 2017;43(1):59–68.

[12] Yatsunenko T, Rey FE, Manary MJ, et al. Human gut microbiome viewed across age and geography. Nature. 2012;486(7402):222–227.

[13] Wu GD, Chen J, Hoffmann C, et al. Linking long-term dietary patterns with gut microbial enterotypes. Science. 2011;334(6052):105–108.

[14] Wingler K, Howard AG, Sha W, et al. Recent urbanization in China is correlated with a westernized microbiome encoding increased virulence and antibiotic resistance genes. Microbiome. 2017 [cited 2017 Nov 26];5(1):121. DOI:10.1186/s40168-017-0338-7.

[15] De Filippo C, Cavalieri 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 U S A. 2010;107(33):14691–14696.

[16] Suez J, Korem T, Zeevi D, et al. Artificial sweeteners induce glucose intolerance by altering the gut microbiota. Nature. 2014;514(7521):181–186.

[17] Ahern PP, Faith JJ, Gordon JL. Mining the human gut microbiota for effector strains that shape the immune system. Immunity. 2014;40(6):815–823.

[18] Ashida H, Ogawa M, Kim M, et al. Bacteria and host interactions in the gut epithelial barrier. Nat Chem Biol. 2011;8(1):36–45.

[19] Diaz Heijtz R, Wang S, Anuar F, et al. Normal gut microbiota modulates brain development and behavior. Proc Natl Acad Sci U S A. 2011;108(7):3047–3052.

[20] Karczykowski J, Troost FJ, Konings I, et al. Regulation of human epithelial tight junction proteins by Lactobacillus plantarum in vivo and protective effects on the epithelial barrier. Am J Physiol Gastrointest Liver Physiol. 2010;298(6):G851–859.

[21] Kelly CJ, Zheng L, Campbell EL, et al. Crosstalk between microbiota-derived short-chain fatty acids and intestinal epithelial HIF augments tissue barrier function. Cell Host Microbe. 2015;17(5):662–671.

[22] Walker WA. The importance of appropriate initial bacterial colonization of the intestine in newborn, child, and adult health. Pediatr Res. 2017;82(3):387–395.

[23] Gomez de Aguero M, Ganal-Vonarburg SC, Fuhrer T, et al. The maternal microbiota drives early postnatal innate immune development. Science. 2016;351(6279):1296–1302.

[24] Wekerle H. The gut-brain connection: triggering of brain autoimmunity disease by commensal gut bacteria. Rheumatology (Oxford). 2016;55(Suppl 2):i68–ii75.

[25] Furusawa Y, Obata Y, Fukuda S, et al. Commensal microbiota-derived butyrate induces the differentiation of colonic regulatory T cells. Nature. 2013;504(7480):446–450.

[26] Arpaia N, Campbell C, Fan X, et al. Metabolites produced by commensal bacteria promote peripheral regulatory T-cell generation. Nature. 2013;504(7480):451–455.

[27] Stecher B, Hardt WD. The role of microbiota in infectious disease. Trends Microbiol. 2008;16(3):107–114.

[28] Macfarlane S, Steed H, Macfarlane GT. Intestinal bacteria and inflammatory bowel disease. Crit Rev Clin Lab Sci. 2009;46(1):25–54.

[29] Erny D, Hrabe de Angelis AL, Jaitin D, et al. Host microbiota constantly control maturation and function of microglia in the CNS. Nat Neurosci. 2015;18(7):965–977.

[30] Mangalam A, Shahi SK, Luckey D, et al. Human gut-derived commensal bacteria suppress CNS inflammatory and demyelinating disease. Cell Rep. 2017;20(6):1269–1277.

[31] Principi N, Esposito S. Gut microbiota and central nervous system development. J Infect. 2016;73(6):536–546.

[32] Hsiao YE, McBride SW, Hsien S, et al. Microbiota modulate behavioral and physiological abnormalities associated with neurodevelopmental disorders. Cell. 2013;155(7):1451–1463.

[33] Khan AA, Khan Z, Malik A, et al. Colorectal cancer-inflammatory bowel disease nexus and fecalon of Escherichia coli. Life Sci. 2017;180:60–67.

[34] Srivastava A, Gupta J, Kumar S, et al. Gut biofilm forming bacteria in inflammatory bowel disease. Microb Pathog. 2017;112:15–14.

[35] Ni J, Wu GD, Alenberg L, et al. Gut microbiota and IBD: causation or correlation? Nat Rev Gastroenterol Hepatol. 2017;14(10):573–584.

[36] Wen L, Duffy A. Factors influencing the gut microbiota, inflammation, and type 2 diabetes. J Nutr. 2017;147(1468S–1475S).

[37] Araujo JR, Tomas J, Brenner C, et al. Impact of high-fat diet on the intestinal microbiota and small intestinal physiology before and after the onset of obesity. Biochimie. 2017;141:97–106.

[38] Seganfredo FB, Blume CA, Moehlecke M, et al. Weight-loss interventions and gut microbiota changes in overweight and obese patients: a systematic review. Obes Rev. 2017;18(8):832–851.

[39] Zeisel SH, Warrier M. Trimethylamine n-oxide, the microbiome, and heart and kidney disease. Annu Rev Nutr. 2017;37:157–181.

[40] Lippi G, Danese E, Mattiuzzi C, et al. The intriguing link between the intestinal microbiota and cardiovascular disease. Semin Thromb Hemost. 2017;43(6):609–613.

[41] Tang WH, Kitai T, Hazen SL. Gut microbiota in cardiovascular health and disease. Circ Res. 2017;120(7):1183–1196.

[42] McKenzie C, Tan J, Macia L, et al. The nutrition-gut microbiome-physiology axis and allergic diseases. Immunol Rev. 2017;278(1):277–295.

[43] Knaysi G, Smith AR, Wilson JM, et al. The skin as a route of allergen exposure: Part II. allergens and role of the microbiome. J Investig Dermatol Symp Proc. 2017;28(1):1–9.

[44] Tan J, Mckenzie C, Vuillermin PJ, et al. Dietary fiber and bacterial SCFA enhance oral tolerance and protect against food allergy through diverse cellular pathways. Cell Rep. 2016;15(12):2809–2824.

[45] Tremlett H, Bauer KC, Appel-Cresswell S, et al. The gut microbiome in human neurological disease: a review. Ann Neurol. 2017;81(3):369–382.

[46] Dahlhamer JM, Zammitti EP, Ward BW, et al. Prevalence of inflammatory bowel disease among adults aged ≥18...
years — United States, 2015. MMWR. 2016;65(42):1166–1169.

[47] Jostins L, Ripke S, Weersma RK, et al. Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease. Nature. 2012;491(7422):119–124.

[48] Machiels K, Joossens M, Sabino J, et al. A decrease of the butyrate-producing species Roseburia hominis and Faecalibacterium prausnitzii defines dysbiosis in patients with ulcerative colitis. Gut. 2014;63(8):1275–1283.

[49] Lepage P, Hasler R, Spehlmann ME, et al. Twin study indicates loss of interaction between microbiota and mucosa of patients with ulcerative colitis. Gastroenterology. 2011;141(1):227–236.

[50] SeksiK P, Rigottier-Gois L, Gramet G, et al. Alterations of the dominant faecal bacterial groups in patients with Crohn’s disease of the colon. Gut. 2003;52(2):237–242.

[51] Joossens M, Huys G, Cnockaert M, et al. Dysbiosis of the faecal microbiota in patients with Crohn’s disease and their unaffected relatives. Gut. 2011;60(5):631–637.

[52] Wu J, Ji A, Wang X, et al. MicroRNA-195-5p, a new regulator of Fra-1, suppresses the migration and invasion of prostate cancer cells. J Transl Med. 2015 [cited 2017 Nov 26];13:289. DOI:10.1186/s12967-015-0650-6.

[53] Mozaffarian D, Hao T, Rimm EB, et al. Changes in diet and lifestyle and long-term weight gain in women and men. N Engl J Med. 2011;364(25):2392–2404.

[54] Ridaura VK, Faith JJ, Rey FE, et al. Gut microbiota from twins discordant for obesity modulate metabolism in mice. Science. 2013 [cited 2017 Nov 26];341(6150):1241214. DOI:10.1126/science.1241214.

[55] Wen L, Ley RE, Volchkov PY, et al. Innate immunity and intestinal microbiota in the development of Type 1 diabetes. Nature. 2008;455(7216):1109–1113.

[56] Larsen N, Vogensen FK, van den Berg FW, et al. Gut microbiota in human adults with type 2 diabetes differs from non-diabetic adults. PLoS One. 2010 [cited 2017 Nov 26];5(2):e9085. DOI:10.1371/journal.pone.0009085.

[57] Forsythe P, Sudo N, Dinan T, et al. Mood and gut feelings. Brain Behav Immun. 2010;24(1):9–16.

[58] Al-Asmakh M, Anuar F, Zadjali F, et al. Gut microbial communities modulating brain development and function. Gut Microbes. 2012;3(4):366–373.

[59] Cryan JF, O’Mahony SM. The microbiome-gut-brain axis: from bowel to behavior. Neurogastroenterol Motil. 2011;23(3):187–192.

[60] Cryan JF, Dinan TG. Mind-altering microorganisms: the impact of the gut microbiota on brain and behaviour. Nat Rev Neurosci. 2012;13(10):701–712.

[61] Montiel-Castro AJ, Gonzalez-Cervantes RM, Bravo-Ruiseco G, et al. The microbiota-gut-brain axis: neurobehavioral correlates, health and sociality. Front Integr Neurosci. 2013 [cited 2017 Nov 26];7:70. DOI:10.3389/fnint.2013.00070.

[62] Farmer AD, Randall HA, Aziz Q. It’s a gut feeling: how the gut microbiota affects the state of mind. J Physiol. 2014;592(14):2981–2988.

[63] Tillisch K. The effects of gut microbiota on CNS function in humans. Gut Microbes. 2014;5(3):404–410.

[64] Wang Y, Kasper LH. The role of microbiome in central nervous system disorders. Brain Behav Immun. 2014;38:1–12.

[65] Lee SH, de La Serred CB. Gut microbiome-brain communications regulate host physiology and behavior. J Nutrition Health Food Sci. 2015 [cited 2017 Nov 26];3(2):1–12. [12 p.] DOI:10.15226/jnhfs.2015.00141.

[66] Doenys C. Gut microbiota, inflammation, and probiotics on neural development in autism spectrum disorder. Neuroscience. 2018;374:271–286.

[67] Newell C, Bomhof MR, Reimer RA, et al. Ketogenic diet modifies the gut microbiota in a murine model of autism spectrum disorder. Mol Autism. 2016 [cited 2017 Nov 26];7(1):37. DOI:10.1186/s13229-016-0099-3.

[68] Vuong HE, Hsiao EY. Emerging roles for the gut microbiome in autism spectrum disorder. Biol Psychiatry. 2017;81(5):411–423.

[69] Li H, Wei C. Diet, gut microbiota and obesity. J Nutrition. 2015;135(9 Suppl):S1:32–40.

[70] Rosen CE, Palm NW. Functional classification of the gut microbiota: the key to cracking the microbiota composition code: functional classifications of the gut microbiota reveal previously hidden contributions of indigenous gut bacteria to human health and disease. BioEssays. 2017 [cited 2017 Nov 26];39(12):DOI:10.1002/bies.201700032.

[71] Long SL, Gahan CGM, Joyce SA. Interactions between gut bacteria and bile in health and disease. Mol Aspects Med. 2017;56:54–65.

[72] Wahlestrom A, Kovatcheva-Datchary P, Stahlman M, et al. Crosstalk between bile acids and gut microbiota and its impact on farnesoid X receptor signalling. Dig Dis. 2017;35(3):246–250.

[73] Buie T, Fuchs GJ 3rd, Furuta GT, et al. Recommendations for evaluation and treatment of common gastrointestinal problems in children with ASDs. Pediatrics. 2010;125(Suppl 1):S19–S29.

[74] Frye RE, Rose S, Slattery J, et al. Gastrointestinal dysfunctions in autism spectrum disorder: the role of the mitochondria and the enteric microbiome. Microb Ecol Health Dis. 2015 [cited 2017 Nov 26];26:27458. DOI:10.3402/mehd.v26.27458.

[75] Ding HT, Taur Y, Walkup JT. Gut microbiota and autism: key concepts and findings. J Autism Dev Disord. 2017;47(2):480–489.