World Journal of Translational Medicine

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5528/wjtm.v3.i3.133

World J Transl Med 2014 December 12; 3(3): 133-140
ISSN 2220-6132 (online)

REVIEW

Pathophysiological responses from human gut microbiome

Anindya Roy Chowdhury, Utpal Bakshi

Anindya Roy Chowdhury, Utpal Bakshi, Structural Biology and Bioinformatics Division, CSIR-Indian Institute of Chemical Biology, Kolkata 700032, India
Author contributions: Roy Chowdhury A designed the study, wrote the manuscript; Bakshi U contributed to the writing of the manuscript.
Supported by University Grants Commission (India) (Bakshi U)
Correspondence to: Dr. Anindya Roy Chowdhury, Structural Biology and Bioinformatics Division, CSIR-Indian Institute of Chemical Biology, 4, Raja S. C. Mullick Road, Kolkata 700032, India. ani.rc.29@gmail.com
Telephone: +91-33-24995875 Fax: +91-33-24735197
Received: June 16, 2014 Revised: August 21, 2014
Accepted: September 18, 2014
Published online: December 12, 2014

Abstract

The human gastrointestinal tract harbors a vast collection of symbiotic microorganisms-collectively termed as "gut microbiome". This microbiota has important effect in immune system and other host activities. Recent studies have suggested that alterations of the normal gut microbiota are associated with various human diseases and psychological disorders. The underlying cause, once proven, may provide novel insights into the importance of gut flora in human health. In this review, we give an attempt to describe how the alteration in the microbial community causes the development of certain widespread pathophysiological disorders; focusing on inflammatory bowel disease, colorectal cancer, obesity and autism. Proper knowledge about the host-microbiota interaction and linkage could be essential for the development of future personalized strategies of therapeutics.

Key words: Human gut microbiome; Inflammatory bowel disease; Colorectal cancer; Obesity; Autism

Core tip: This review is an endeavor to provide an account about the human gut microbiome, their diversity, and disease causing capability. Till date, so many diseases have been associated with the alteration of gut microbiota. In this review we talk about four of the major diseases/disorders, *viz.*, inflammatory bowel disease, colorectal cancer, obesity and autism.

Roy Chowdhury A, Bakshi U. Pathophysiological responses from human gut microbiome. *World J Transl Med* 2014; 3(3): 133-140 Available from: URL: http://www.wjgnet.com/2220-6132/full/v3/i3/133.htm DOI: http://dx.doi.org/10.5528/wjtm.v3.i3.133

INTRODUCTION

The topic of human microbiome is pretty trendy in the present world of science. Human body is inhabited by more microbial cells than our own cell numbers. The term "microbiome" refers to the whole number of microorganisms residing in human body and their genetic material[1-3]. It is different from the term "microbiota", which describes the microbial population present in different niches in the body. Resident microbes contain ten times more cells than our own somatic and germ cells and hence more number of genes than present in a human body-as a consequence they represent a combined microbial genome with a size bigger than human genome itself[1,4]. Collectively, the flora has a metabolic action equal to a virtual organ within an organ[5]. Researchers at human microbiome project, NIH are sampling and exploring data from few specific sites of human body, *viz.*, airways, nasal passages, oral cavities, skin, blood, gastrointestinal tract, and urogenital tract[2]. The microbial density starts increasing in the distal small intestine, and in the large intestine it rises to an estimated of 10^{11}-10^{12} microbes per gram of colonic content, which contributes to 60% of the fecal mass. However, this is to bear in mind, since so many factors affect our body's ecosystem, the microbiota composition is different for every individual regardless of their age and sex.

Usually this microbiota is commensal and represents a healthy asset of our body, helping us to digest food and maintain immunity. Our typical understanding about a disease causing event states us that whenever a pathogenic organism enters our body, the disease takes shape. Introduction to the era of human microbiome enlightens us about a more susceptible way of causing disease-the imbalance of the microbiota within our body. Therefore human microbiome can be considered as a therapeutic drug target[6].

The organisms from this microbiome are hard to culture. Metagenomics, the study of the genetic material extracted directly from environmental samples in a given environment, has been applied to the studies of the human microbiome, since it can be used to investigate various microbes simultaneously, without cultivation. This approach gathers speed in studies of human microbiome and their medical relevance. Studies about diverse microbes from the human body site-specific microbiota, and the correlations between their composition and disease have rapidly increased our understanding towards the importance of the human microbiome and its roles in health and disease[3,7]. This bang of human microbiome data holds the promise of managing personal health, based on the genome and microbiome information of an individual.

HUMAN GUT MICROBIOME

A new chapter in medical science has emerged with the recognition of the crucial role of the gut microbiota in health and disease. At the time of birth human gut is completely sterile. However, immediately after birth the colonization of mammoth variety of microorganisms including bacteria, archaea, fungi and viruses starts within the body. The colonization of these microbial species within a body depends upon the mode of delivery, hygene level, infant diet, and medication[8].

Among all the niches, human GI tract contains the most number of microorganisms. The density of the microbiota increases from the proximal to the distal gut, reaching its maximum at the colon. In the different habitats of the gut, ecological sorting and competitive exclusion between microbes are the key factors influencing microbial diversity[9,10]. Stochastic factors during colonization and in situ evolution cause the diversity of gut microbiota between individuals[11]. The intestinal microbiota of infants lacks diversity and the major constituents are the phyla *Proteobacteria* and *Actinobacteria*. The microbiota attains diversity with age with the addition of *Fusobacteria*, *Cyanobacteria*, *Verrucomicrobia* and *Actinobacteria* amongst others and the dominance of *Firmicutes* and *Bacteroidetes* characterizes the adult microbiota[12-14]. The gut microbiota is mainly a collection of anaerobes, which outnumber facultative anaerobes and aerobic microbes by approximately 2-3 orders of magnitude[15]. In human, after the age of 2.5 years the gut microbiota remains almost the same throughout the adult age of that individual[16,17]. The actual adult human gut microbiota composition is diverse and differs from person to person in a significant way. Therefore it has been suggested that it can be used as a substitute to fingerprinting[18]. In this regard three enterotypes have been found, *viz., Prevotella*, *Ruminococcus* and *Bacteroids* that are independent of age or sex. The normal human gut flora composition is subject to age, diet, medication and socioeconomic conditions. In a recent study of gut microbiota in elderly individuals, the associations with diet and age was documented[19].

It is a prominent fact that, although there is great variety in the composition of the gut microbiota among individuals, there still lays a conserved set shared between individuals, and this set of microbiota is called the core gut microbiome[20]. The functions and pathways encoded by the core gut microbiome offer the greatest benefit to the host and are essential for the correct functioning of the healthy gut. The gut microbiota helps the host in various ways, including protection against probable pathogens, production of essential vitamins, digestion of polysaccharides, regulation of fat storage and modulation of the host's immune system[21]. Latest studies have also revealed that the gut microbiota influences brain and the gut-brain axis configures the stress related symptoms such as anxiety and pain tolerance and few other psychological condition[22].

ROLE OF GUT MICROBIOTA IN HUMAN DISEASE/DISORDER

It has been well established that the human gut microbiota is essential for human health. However, an alteration of the normal composition of the gut microbiome leads to formation of various types of diseases. Therefore it is reasonable to conclude that modulation of the gut microbiota can be used as a therapeutic target in treating these chronic diseases. Before properly utilizing the gut microbiota as a therapeutic tool, it is necessary to understand the role of these microbes in shaping disease. Till date, a great number of physical and psychological disorders have been associated with the alteration of gut flora; addressing all can be quite unfeasible task for this review. Thus, in this review, brief overviews of the current understanding about the role of microbiota in four common disease and disorders have been discussed.

INFLAMMATORY BOWEL DISEASE

Inflammatory bowel disease (IBD) is chronic, relapsing, immunologically mediated disorder that affects the digestive tract, mainly colon and small intestine. IBD majorly includes ulcerative colitis (UC) and Crohn's disease (CD). There is considerable evidence suggesting the importance of gut microbiota in IBD[23-25]. Recent studies imply that an unbalanced microbial community composition is associated with a dysregulated immune response[26]. Although the exact mechanism of IBD is not yet being

fully elucidated, four broad mechanisms are proposed to explain the complex relationship between the commensal microbiota and IBD: (1) dysbiosis of conventional microbiota; (2) induction of intestinal inflammation by pathogens and functionally altered commensal bacteria; (3) host genetic defects in containing commensal microbiota; and (4) defective host immunoregulation[27]. The net result of these effects is continuous antigenic stimulation that activates pathogenic T cells, ultimately causing chronic intestinal inflammation. In case of patients suffering from CD, intestinal T lymphocytes have shown to be hyperactive against bacterial antigens as local tolerant mechanism is found to be abolished in them[28]. In addition, they have increased intestinal secretion of IgG antibodies against a broad spectrum of commensal bacteria that, unlike IgA, activate complement cascade and inflammatory mediators[29,30].

There are various hypothesis of how microbial composition in human gut plays vital role in the pathogenesis of IBD. Recent studies have shown that reduction of dominant commensal bacteria, such as *Firmicutes* and *Bacteroidetes*, and an increased number of *Proteobacteria* and *Actinobacteria*, may lead to this pathophysiological condition of human gut[31,32]. A wide variety of gut microbial species have directly being linked with IBD. Among Firmicutes, *Faecalibacterium prausnitzii* is shown to have anti inflammatory activity and is found to be significantly decreased in CD[33,34]. Furthermore, Joossens *et al*[35] have shown that reduction of *Faecalibacterium prausnitzii*, *Bifidobacterium adolescentis*, *Dialister invisus*, an unknown species of *Clostridium* clusters XIVA and increase of *Ruminococcus gnavus* are characteristic features in patients suffering from CD. A number of studies have shown that a wide variety of probiotic microorganisms, including *Escherichia coli, Saccharomyces boulardii*, and *Bifidobacterium* are involved in treating UC, although these are not always supported by high quality clinical trials[36-42]. Also the role of microbiota in fecal transplantation, efficiently utilized in severe *Clostridium difficile* infection, have shown to be effective in IBD[43,44].

COLORECTAL CANCER

Colorectal cancer (CRC) is one of the most common malignancies in the world, which accounts for about half million deaths annually[45]. Although the prevalence of CRC is higher in the western world but it is found to be increasing in the developing countries at an alarming pace. Two principle mechanisms are mainly involved for the development of CRC-molecular genetics mechanisms and environmental factors[46]. Dietary and genetic factors interact with each other *via* events taking place in the lumen of the large intestine[47].

The genetic mechanisms of CRC are well established[48]. A number of oncogenes and tumor-suppressor genes, such as *APC*, *KRAS*, *p53* and other regulatory genes are mutated in CRC patients. Together with DNA-methylation and chromatin-structure changes, the mutations act to dysregulate conserved signaling networks that play vital role on cell phenotypes, including the regulation of cellular metabolism, proliferation, differentiation, and survival. Beside genes, environmental factors also influence the occurrence of CRC. Dietary carbohydrate and fat play critical roles in the development of colon tumorigenesis[49]. Studies suggested that dietary fat and high consumption of red meat are associated with high risk of CRC[50]. By contrast, a high intake of complex carbohydrate or dietary fibers, such as cellulose, lignin and pectin, that undergo bacterial fermentation in the colon, has been associated with reduced CRC risk[51-53].

The effect of diet on carcinogenic process is mediated by changes in metabolic activity and composition of the colonic microbiome that accounts for over 100 trillion bacteria grouped in about 1000 species in human gut[54,55]. Various studies have shown significant association between abundance of different bacterial species, particularly *Fusobacterium nucleatum*, with the prevalence of CRC[56,57]. CRC risk was found to be associated with decreased bacterial diversity of Gram-positive, fiber-fermenting Clostridia; and increased presence of Gram-negative, pro-inflammatory genera such as *Fusobacterium* and *Porphyromonas*[58]. The bacterial gut population can be shifted to a healthier composition by dietary fiber that provides substrates for bacterial fermentation[55]. On the other hand, diet rich in fat and meat but poor in vegetables increases the concentration of N-nitroso compounds, a group of genotoxic substances that are known initiators of colon cancer[59]. Another group of carcinogens are heterocyclic aromatic amines that are found in meat and some intestinal bacteria leads to DNA damage in colon cells due to the presence of such compounds[60]. A more descriptive human study highlighted that high risk of CRC is associated with the presence of *Bacteroides vulgatus* and *Bacteroides stercoris*, whereas presence of *Lactobacillus acidophilus*, *Lactobacillus S06* and *Eubacterium aerofaciens* are associated with low risk of CRC[61]. Although there is no conclusive evidence, gut microbiome seems to be a significant contributing factor that modulates risk of CRC in human beings.

OBESITY

Obesity is a medical disorder in which excess body fat accumulates over body. It is only recently that the problem of obesity has achieved global acknowledgment, in contrast to the problem of underweight and malnutrition-which have always conquered clinical attention. World Health Organization describes obesity as one of the major public health concern that threatens the modern world civilization and of late has become a global epidemic. A person is categorized as overweight when the body-mass index (BMI) is around 25 kg/m^2 or higher and people are classified as obese when the BMI is 30 kg/m^2 or more[62]. A plentiful of studies has demonstrated that obese individuals are lazy, lack self-discipline. There is a social disgrace and discrimination against obese people

in various fields of life, which in turn creates numerous consequences for their psychological and to some extent physical health[63]. However, obesity is not only a cosmetic concern. It has serious health concerns including increased risk for type 2 diabetes, cardiovascular diseases, non alcoholic fatty liver disease, pulmonary hypertension, asthma, sleep apnea, osteoarthritis, gall-bladder disease, a number of cancers, and most importantly an increased risk of mortality[64].

Numerous studies have suggested that the gut microbiota plays a crucial role in the development of fat mass and altered energy homeostasis[65]. Obese gut microbiota increases both the capacity to harvest energy from the diet and the accumulation of fat in adipose tissue and liver, by altering host metabolism. Studies in germ-free and conventionalized mice revealed that the microbiota helps in absorbing the monosaccharides from the gut lumen and adipocyte hypertrophy by suppressing fasting-induced adipocyte factor in the intestine, and this suggests that the gut microbiota is an important factor that affects energy harvest from the diet and energy storage in the host[66,67]. The gut microbial community is diverse; consisting of bacterial species, archaea and various microbial eukaryotes. Therefore competitive interactions among these species might also play crucial roles in promoting obesity. In this regard, methane producing archaea *Methanobrevibacter smithi* has been found to be present in greater abundance in obese mice and humans when compared with lean individuals[68,69]. Obesity and diet could be associated with altered gut microbiota characterized by a high *Firmicutes* to *Bacteroidetes* ratio and a dramatic fall in overall microbial diversity[70].

It has been proposed that the composition of the gut microbiota during childhood predicts the following development of obesity in humans. In this regard some studies were conducted to compare between the fecal samples from overweight/obese and normal weight children[68,71]. It shows that during infancy, a significantly higher number of *Bifidobacterial* species was observed in children who maintain a normal weight at age 7 years, while significantly greater numbers of *Staphylococcus aureus* were detected in children who became obese afterward. Therefore, it is hypothesized that an early modulation of gut microbiota can actually prevent obesity[72,73]. Interestingly, another study found that the microbiota composition is different in case of pregnant women also, with relatively higher numbers of *Bacteroides* and *Staphylococcus* found in overweight pregnant women[74]. Obese human twins also have different gut microbial composition as compared to their lean twin. The obese one has reduced levels of *Bacteroidetes* and also less bacterial diversity[69].

AUTISM

The brain is strongly coupled with the gut *via* 200-600 million neurons[75]. Currently, a growing number of clinical data and experimental observations suggest the presence of bidirectional gut-brain axis, implying that there are probably many a type of neuro-atypical symptoms; including stress, depression, anxiety, associated with the alteration of the normal composition of gut microbial flora[76,77]. In this review we would like to restrict ourselves to one neuropsychiatric disorder-Autism. The Autism Spectrum Disorder (ASD) is an assemblage of neuro-developmental disorders characterized by obscurity in social interaction and communication in affected children. It is typically associated with limited, repetitive, and stereotypic behavior and is noticeable within the first 3 years of life[78,79]. Until 1990, Autism was treated as a rare psychological disorder. Today it is a major health concern, big emotional burden for families, and large financial burden for the government worldwide.

Though the principal cause of this disorder is yet to be known; gastrointestinal disorders have frequently been reported in the children with autism-suggesting the probable link between the atypical compositions of human gut microbiome with ASD[80]. The hypothesis regarding the gut microbiota and ASD linkage was first coined by Bolte[81]. Their study showed that interruption in the normal composition of native gut flora resulted colonization of some neurotoxin producing bacteria, contributing to the autistic symptom[82]. As the importance of gut microbiota in gut-brain function came emerging; probable role of diet, bacteria, and enzyme became a field of important study in autism research[83]. It has been proved that there is a significant difference between the stool sample from autistic and normal children in terms of frequency of occurence of four bacterial phyla specifically, *viz., Firmicutes, Bacteroids, Actinobacteria* and *Proteobacteria*. Further studies have shown higher count and diversity of *Clostridia* (mainly *Clostridium tetani*, *Clostridium perfringens* and *Clostridium bolteae*) and *Desulfovibrio* (mainly *D.desulfuricans*, *D.fairfieldensis*, *D.piger*) in fecal samples of children with autistic behavior as compared to the normal healthy children with same sex and age[81,84-91]. Evidence suggests that high occurrence of *Bifidobacterium* and *Lactobacillus* species is a biological indicator for healthy gut microbiota in breast-fed infants as they serve important probiotic function in the gut[92-94]. As expected, these organisms are frequently reported to be lower in patients with ASD. People are working with several animal models to investigate the expected link between gut microbiota and autism like disorders. One recent paper on maternal immune activation (MIA) mouse model has revealed gastrointestinal abnormalities and changes in the gut microbial community in offspring of MIA animals with autism-like symptoms[95].

Till date, several studies have demonstrated the presence of a perturbed intestinal microbiota composition in children with ASD compared to normal control children. However, caution should be applied while drawing conclusion from these results, as patients with ASD have probable history of using high antibiotic dosage and different diets compared with neuro-typical individuals, either of these can influence the normal composition of the gut microbiota[96,97]. Fortunately enough, a recent study demonstrated that the alteration in the concentra-

tions of short-chain fatty acids in the fecal sample of children with ASD[98]. This suggests that atypical production of such microbial metabolites may have a direct effect on our brain function and thus bacteria can modulate the brain function in a straight line.

CONCLUSION

It is well established fact that the gut microbiota influences host metabolism, immune function, and host homeostasis. Interruption in this balanced community may generate very serious health troubles for the host. Advancement of next-generation genomic technology will pave the way to the development of experimental models of representative examples from the human gut microbiome. This will consecutively accelerate the discovery, testing, and validation of novel drug targets. Future metagenomic research is also expected to focus on the complex relationships of the gut microbiome composition and host metabolism so that in time their actual importance to human health will also be understood better. More in depth understanding of the specific relationships between the gut microbiota and disease will enlighten us about the potential therapeutic targets. The issue of intelligent modulation of the intestinal community is a topic of great interest nowadays. The gut microbiome is expected to contribute immensely to the delivery of personalized healthcare strategies that are already being applied into the clinical environment for the benefit of patients. It can open new door to treating disease and potential modulation of human disease risk factors.

ACKNOWLEDGMENTS

The authors report no potential conflicts of interest.

REFERENCES

1 **Human Microbiome Project Consortium**. Structure, function and diversity of the healthy human microbiome. *Nature* 2012; **486**: 207-214 [PMID: 22699609 DOI: 10.1038/nature11234]

2 **Peterson J**, Garges S, Giovanni M, McInnes P, Wang L, Schloss JA, Bonazzi V, McEwen JE, Wetterstrand KA, Deal C, Baker CC, Di Francesco V, Howcroft TK, Karp RW, Lunsford RD, Wellington CR, Belachew T, Wright M, Giblin C, David H, Mills M, Salomon R, Mullins C, Akolkar B, Begg L, Davis C, Grandison L, Humble M, Khalsa J, Little AR, Peavy H, Pontzer C, Portnoy M, Sayre MH, Starke-Reed P, Zakhari S, Read J, Watson B, Guyer M. The NIH Human Microbiome Project. *Genome Res* 2009; **19**: 2317-2323 [PMID: 19819907 DOI: 10.1101/gr.096651.109]

3 **Turnbaugh PJ**, Ley RE, Hamady M, Fraser-Liggett MC, Knight R, Gordon JI. The human microbiome project: exploring the microbial part of ourselves in a changing world. *Nature* 2007; **449**: 804-810 [DOI: 10.1038/nature06244]

4 **Shanahan F**. The host-microbe interface within the gut. *Best Pract Res Clin Gastroenterol* 2002; **16**: 915-931 [PMID: 12473298]

5 **Bocci V**. The neglected organ: bacterial flora has a crucial immunostimulatory role. *Perspect Biol Med* 1992; **35**: 251-260 [PMID: 1557302]

6 **Wallace BD**, Redinbo MR. The human microbiome is a source of therapeutic drug targets. *Curr Opin Chem Biol* 2013; **17**: 379-384 [PMID: 23680493 DOI: 10.1016/j.cbpa.2013.04.011]

7 **Costello EK**, Lauber CL, Hamady M, Fierer N, Gordon JI, Knight R. Bacterial community variation in human body habitats across space and time. *Science* 2009; **326**: 1694-1697 [PMID: 19892944 DOI: 10.1126/science.1177486]

8 **Grönlund MM**, Lehtonen OP, Eerola E, Kero P. Fecal microflora in healthy infants born by different methods of delivery: permanent changes in intestinal flora after cesarean delivery. *J Pediatr Gastroenterol Nutr* 1999; **28**: 19-25 [PMID: 9890463]

9 **Benson AK**, Kelly SA, Legge R, Ma F, Low SJ, Kim J, Zhang M, Oh PL, Nehrenberg D, Hua K, Kachman SD, Moriyama EN, Walter J, Peterson DA, Pomp D. Individuality in gut microbiota composition is a complex polygenic trait shaped by multiple environmental and host genetic factors. *Proc Natl Acad Sci USA* 2010; **107**: 18933-18938 [PMID: 20937875 DOI: 10.1073/pnas.1007028107]

10 **Ley RE**, Peterson DA, Gordon JI. Ecological and evolutionary forces shaping microbial diversity in the human intestine. *Cell* 2006; **124**: 837-848 [PMID: 16497592]

11 **Walter J**, Ley R. The human gut microbiome: ecology and recent evolutionary changes. *Annu Rev Microbiol* 2011; **65**: 411-429 [PMID: 21682646 DOI: 10.1146/annurev-micro-090110-102830]

12 **Bäckhed F**. Programming of host metabolism by the gut microbiota. *Ann Nutr Metab* 2011; **58** Suppl 2: 44-52 [PMID: 21846980 DOI: 10.1159/000328042]

13 **Eckburg PB**, Bik EM, Bernstein CN, Purdom E, Dethlefsen L, Sargent M, Gill SR, Nelson KE, Relman DA. Diversity of the human intestinal microbial flora. *Science* 2005; **308**: 1635-1638 [PMID: 15831718]

14 **Qin J**, Li R, Raes J, Arumugam M, Burgdorf KS, Manichanh C, Nielsen T, Pons N, Levenez F, Yamada T, Mende DR, Li J, Xu J, Li S, Li D, Cao J, Wang B, Liang H, Zheng H, Xie Y, Tap J, Lepage P, Bertalan M, Batto JM, Hansen T, Le Paslier D, Linneberg A, Nielsen HB, Pelletier E, Renault P, Sicheritz-Ponten T, Turner K, Zhu H, Yu C, Li S, Jian M, Zhou Y, Li Y, Zhang X, Li S, Qin N, Yang H, Wang J, Brunak S, Doré J, Guarner F, Kristiansen K, Pedersen O, Parkhill J, Weissenbach J, Bork P, Ehrlich SD, Wang J. A human gut microbial gene catalogue established by metagenomic sequencing. *Nature* 2010; **464**: 59-65 [PMID: 20203603 DOI: 10.1038/nature08821]

15 **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 [PMID: 22424233 DOI: 10.1016/j.cell.2012.01.035]

16 **Koenig JE**, Spor A, Scalfone N, Fricker AD, Stombaugh J, Knight R, Angenent LT, Ley RE. Succession of microbial consortia in the developing infant gut microbiome. *Proc Natl Acad Sci USA* 2011; **108** Suppl 1: 4578-4585 [PMID: 20668239 DOI: 10.1073/pnas.1000081107]

17 **Palmer C**, Bik EM, DiGiulio DB, Relman DA, Brown PO. Development of the human infant intestinal microbiota. *PLoS Biol* 2007; **5**: e177 [PMID: 17594176]

18 **Arumugam M**, Raes J, Pelletier E, Le Paslier D, Yamada T, Mende DR, Fernandes GR, Tap J, Bruls T, Batto JM, Bertalan M, Borruel N, Casellas F, Fernandez L, Gautier L, Hansen T, Hattori M, Hayashi T, Kleerebezem M, Kurokawa K, Leclerc M, Levenez F, Manichanh C, Nielsen HB, Nielsen T, Pons N, Poulain J, Qin J, Sicheritz-Ponten T, Tims S, Torrents D, Ugarte E, Zoetendal EG, Wang J, Guarner F, Pedersen O, de Vos WM, Brunak S, Doré J, Antolín M, Artiguenave F, Blottiere HM, Almeida M, Brechot C, Cara C, Chervaux C, Cultrone A, Delorme C, Denariaz G, Dervyn R, Foerstner KU, Friss C, van de Guchte M, Guedon E, Haimet F, Huber W, van Hylckama-Vlieg J, Jamet A, Juste C, Kaci G, Knol J, Lakhdari O, Layec S, Le Roux K, Maguin E, Mérieux A, Melo Minardi R, M'rini C, Muller J, Oozeer R, Parkhill J, Renault

P, Rescigno M, Sanchez N, Sunagawa S, Torrejon A, Turner K, Vandemeulebrouck G, Varela E, Winogradsky Y, Zeller G, Weissenbach J, Ehrlich SD, Bork P. Enterotypes of the human gut microbiome. *Nature* 2011; **473**: 174-180 [PMID: 21508958 DOI: 10.1038/nature09944]

19 **Claesson MJ**, Jeffery IB, Conde S, Power SE, O'Connor EM, Cusack S, Harris HM, Coakley M, Lakshminarayanan B, O' Sullivan O, Fitzgerald GF, Deane J, O'Connor M, Harnedy N, O'Connor K, O'Mahony D, van Sinderen D, Wallace M, Brennan L, Stanton C, Marchesi JR, Fitzgerald AP, Shanahan F, Hill C, Ross RP, O'Toole PW. Gut microbiota composition correlates with diet and health in the elderly. *Nature* 2012; **488**: 178-184 [PMID: 22797518 DOI: 10.1038/nature11319]

20 **Turnbaugh PJ**, Gordon JI. The core gut microbiome, energy balance and obesity. *J Physiol* 2009; **587**: 4153-4158 [PMID: 19491241 DOI: 10.1113/jphysiol.2009.174136]

21 **Sekirov I**, Russell SL, Antunes LC, Finlay BB. Gut microbiota in health and disease. *Physiol Rev* 2010; **90**: 859-904 [PMID: 20664075 DOI: 10.1152/physrev.00045.2009]

22 **Cryan JF**, O'Mahony SM. The microbiome-gut-brain axis: from bowel to behavior. *Neurogastroenterol Motil* 2011; **23**: 187-192 [PMID: 21303428 DOI: 10.1111/j.1365-2982.2010.01664.x]

23 **Sartor RB**, Muehlbauer M. Microbial host interactions in IBD: implications for pathogenesis and therapy. *Curr Gastroenterol Rep* 2007; **9**: 497-507 [PMID: 18377803]

24 **Shanahan F**. Inflammatory bowel disease: immunodiagnostics, immunotherapeutics, and ecotherapeutics. *Gastroenterology* 2001; **120**: 622-635 [PMID: 11179240]

25 **Shanahan F**. The microbiota in inflammatory bowel disease: friend, bystander, and sometime-villain. *Nutr Rev* 2012; **70** Suppl 1: S31-S37 [PMID: 22861805 DOI: 10.1111/j.1753-4887.2012.00502.x]

26 **Jostins L**, Ripke S, Weersma RK, Duerr RH, McGovern DP, Hui KY, Lee JC, Schumm LP, Sharma Y, Anderson CA, Essers J, Mitrovic M, Ning K, Cleynen I, Theatre E, Spain SL, Raychaudhuri S, Goyette P, Wei Z, Abraham C, Achkar JP, Ahmad T, Amininejad L, Ananthakrishnan AN, Andersen V, Andrews JM, Baidoo L, Balschun T, Bampton PA, Bitton A, Boucher G, Brand S, Büning C, Cohain A, Cichon S, D' Amato M, De Jong D, Devaney KL, Dubinsky M, Edwards C, Ellinghaus D, Ferguson LR, Franchimont D, Fransen K, Gearry R, Georges M, Gieger C, Glas J, Haritunians T, Hart A, Hawkey C, Hedl M, Hu X, Karlsen TH, Kupcinskas L, Kugathasan S, Latiano A, Laukens D, Lawrance IC, Lees CW, Louis E, Mahy G, Mansfield J, Morgan AR, Mowat C, Newman W, Palmieri O, Ponsioen CY, Potocnik U, Prescott NJ, Regueiro M, Rotter JI, Russell RK, Sanderson JD, Sans M, Satsangi J, Schreiber S, Simms LA, Sventoraityte J, Targan SR, Taylor KD, Tremelling M, Verspaget HW, De Vos M, Wijmenga C, Wilson DC, Winkelmann J, Xavier RJ, Zeissig S, Zhang B, Zhang CK, Zhao H, Silverberg MS, Annese V, Hakonarson H, Brant SR, Radford-Smith G, Mathew CG, Rioux JD, Schadt EE, Daly MJ, Franke A, Parkes M, Vermeire S, Barrett JC, Cho JH. Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease. *Nature* 2012; **491**: 119-124 [PMID: 23128233 DOI: 10.1038/nature11582]

27 **Sartor RB**, Mazmanian SK. Intestinal microbes in inflammatory bowel diseases. *Am J Gastroenterol Suppl* 2012; **1**: 15-21 [DOI: 10.1038/ajgsup.2012.4]

28 **Pirzer U**, Schönhaar A, Fleischer B, Hermann E, Meyer zum Büschenfelde KH. Reactivity of infiltrating T lymphocytes with microbial antigens in Crohn's disease. *Lancet* 1991; **338**: 1238-1239 [PMID: 1682646]

29 **Brandtzaeg P**, Halstensen TS, Kett K, Krajci P, Kvale D, Rognum TO, Scott H, Sollid LM. Immunobiology and immunopathology of human gut mucosa: humoral immunity and intraepithelial lymphocytes. *Gastroenterology* 1989; **97**: 1562-1584 [PMID: 2684725]

30 **Macpherson A**, Khoo UY, Forgacs I, Philpott-Howard J, Bjarnason I. Mucosal antibodies in inflammatory bowel disease are directed against intestinal bacteria. *Gut* 1996; **38**: 365-375 [PMID: 8675088]

31 **Fava F**, Danese S. Intestinal microbiota in inflammatory bowel disease: friend of foe? *World J Gastroenterol* 2011; **17**: 557-566 [PMID: 21350704 DOI: 10.3748/wjg.v17.i5.557]

32 **Manichanh C**, Borruel N, Casellas F, Guarner F. The gut microbiota in IBD. *Nat Rev Gastroenterol Hepatol* 2012; **9**: 599-608 [PMID: 22907164 DOI: 10.1038/nrgastro.2012.152]

33 **Sokol H**, Pigneur BD, Watterlot L, Lakhdari O, Bermudez-Humaran LG, Gratadoux JJ, Blugeon S, Bridonneau C, Furet JP, Corthier G, Grangette C, Vasquez N, Pochart P, Trugnan G, Thomas G, Blottiere HM, Dore J, Marteau P, Seksik P, Langella P. Faecalibacterium prausnitzii is an anti-inflammatory commensal bacterium identified by gut microbiota analysis of Crohn disease patients. *P Natl Acad Sci USA* 2008; **105**: 16731-16736 [DOI: 10.1073/pnas.0804812105]

34 **Sokol H**, Seksik P, Furet JP, Firmesse O, Nion-Larmurier I, Beaugerie L, Cosnes J, Corthier G, Marteau P, Doré J. Low counts of Faecalibacterium prausnitzii in colitis microbiota. *Inflamm Bowel Dis* 2009; **15**: 1183-1189 [PMID: 19235886 DOI: 10.1002/ibd.20903]

35 **Joossens M**, Huys G, Cnockaert M, De Preter V, Verbeke K, Rutgeerts P, Vandamme P, Vermeire S. Dysbiosis of the faecal microbiota in patients with Crohn's disease and their unaffected relatives. *Gut* 2011; **60**: 631-637 [PMID: 21209126 DOI: 10.1136/gut.2010.223263]

36 **Bibiloni R**, Fedorak RN, Tannock GW, Madsen KL, Gionchetti P, Campieri M, De Simone C, Sartor RB. VSL#3 probiotic-mixture induces remission in patients with active ulcerative colitis. *Am J Gastroenterol* 2005; **100**: 1539-1546 [PMID: 15984978]

37 **Guslandi M**, Giollo P, Testoni PA. A pilot trial of Saccharomyces boulardii in ulcerative colitis. *Eur J Gastroenterol Hepatol* 2003; **15**: 697-698 [PMID: 12840682]

38 **Ishikawa H**, Akedo I, Umesaki Y, Tanaka R, Imaoka A, Otani T. Randomized controlled trial of the effect of bifidobacteria-fermented milk on ulcerative colitis. *J Am Coll Nutr* 2003; **22**: 56-63 [PMID: 12569115]

39 **Kruis W**, Fric P, Pokrotnieks J, Lukás M, Fixa B, Kascák M, Kamm MA, Weismueller J, Beglinger C, Stolte M, Wolff C, Schulze J. Maintaining remission of ulcerative colitis with the probiotic Escherichia coli Nissle 1917 is as effective as with standard mesalazine. *Gut* 2004; **53**: 1617-1623 [PMID: 15479682]

40 **Kruis W**, Schütz E, Fric P, Fixa B, Judmaier G, Stolte M. Double-blind comparison of an oral Escherichia coli preparation and mesalazine in maintaining remission of ulcerative colitis. *Aliment Pharmacol Ther* 1997; **11**: 853-858 [PMID: 9354192]

41 **Rembacken BJ**, Snelling AM, Hawkey PM, Chalmers DM, Axon AT. Non-pathogenic Escherichia coli versus mesalazine for the treatment of ulcerative colitis: a randomised trial. *Lancet* 1999; **354**: 635-639 [PMID: 10466665]

42 **Zocco MA**, dal Verme LZ, Cremonini F, Piscaglia AC, Nista EC, Candelli M, Novi M, Rigante D, Cazzato IA, Ojetti V, Armuzzi A, Gasbarrini G, Gasbarrini A. Efficacy of Lactobacillus GG in maintaining remission of ulcerative colitis. *Aliment Pharmacol Ther* 2006; **23**: 1567-1574 [PMID: 16696804]

43 **Damman CJ**, Miller SI, Surawicz CM, Zisman TL. The microbiome and inflammatory bowel disease: is there a therapeutic role for fecal microbiota transplantation? *Am J Gastroenterol* 2012; **107**: 1452-1459 [PMID: 23034604 DOI: 10.1038/ajg.2012.93]

44 **Kahn SA**, Gorawara-Bhat R, Rubin DT. Fecal bacteriotherapy for ulcerative colitis: patients are ready, are we? *Inflamm Bowel Dis* 2012; **18**: 676-684 [PMID: 21618362]

45 **Parkin DM**, Pisani P, Ferlay J. Global cancer statistics. *CA Cancer J Clin* 1999; **49**: 33-64, 1 [PMID: 10200776]

46 **Chambers WM**, Warren BF, Jewell DP, Mortensen NJ. Cancer surveillance in ulcerative colitis. *Br J Surg* 2005; **92**: 928-936

[PMID: 16034807]
47 **Rafter J**, Glinghammar B. Interactions between the environment and genes in the colon. *Eur J Cancer Prev* 1998; **7** Suppl 2: S69-S74 [PMID: 9696945]
48 **Fearon ER**. Molecular genetics of colorectal cancer. *Annu Rev Pathol* 2011; **6**: 479-507 [PMID: 21090969 DOI: 10.1146/annurev-pathol-011110-130235]
49 **Kushi LH**, Byers T, Doyle C, Bandera EV, McCullough M, McTiernan A, Gansler T, Andrews KS, Thun MJ. American Cancer Society Guidelines on Nutrition and Physical Activity for cancer prevention: reducing the risk of cancer with healthy food choices and physical activity. *CA Cancer J Clin* 2006; **56**: 254-281; quiz 313-314 [PMID: 17005596]
50 **Bingham SA**. High-meat diets and cancer risk. *P Nutr Soc* 1999; **58**: 243-248 [DOI: 10.1017/S0029665199000336]
51 **Kaczmarczyk MM**, Miller MJ, Freund GG. The health benefits of dietary fiber: beyond the usual suspects of type 2 diabetes mellitus, cardiovascular disease and colon cancer. *Metabolism* 2012; **61**: 1058-1066 [DOI: 10.1016/j.metabol.2012.01.017]
52 **Nomura AM**, Hankin JH, Henderson BE, Wilkens LR, Murphy SP, Pike MC, Le Marchand L, Stram DO, Monroe KR, Kolonel LN. Dietary fiber and colorectal cancer risk: the multiethnic cohort study. *Cancer Causes Control* 2007; **18**: 753-764 [PMID: 17557210]
53 **Peters U**, Sinha R, Chatterjee N, Subar AF, Ziegler RG, Kulldorff M, Bresalier R, Weissfeld JL, Flood A, Schatzkin A, Hayes RB. Dietary fibre and colorectal adenoma in a colorectal cancer early detection programme. *Lancet* 2003; **361**: 1491-1495 [PMID: 12737857]
54 **Floch MH**. Intestinal microecology in health and wellness. *J Clin Gastroenterol* 2011; **45** Suppl: S108-S110 [PMID: 21992947 DOI: 10.1097/MCG.0b013e3182309276]
55 **Zhu Y**, Michelle Luo T, Jobin C, Young HA. Gut microbiota and probiotics in colon tumorigenesis. *Cancer Lett* 2011; **309**: 119-127 [PMID: 21741763 DOI: 10.1016/j.canlet.2011.06.004]
56 **Castellarin M**, Warren RL, Freeman JD, Dreolini L, Krzywinski M, Strauss J, Barnes R, Watson P, Allen-Vercoe E, Moore RA, Holt RA. Fusobacterium nucleatum infection is prevalent in human colorectal carcinoma. *Genome Res* 2012; **22**: 299-306 [PMID: 22009989 DOI: 10.1101/gr.126516.111]
57 **Kostic AD**, Gevers D, Pedamallu CS, Michaud M, Duke F, Earl AM, Ojesina AI, Jung J, Bass AJ, Tabernero J, Baselga J, Liu C, Shivdasani RA, Ogino S, Birren BW, Huttenhower C, Garrett WS, Meyerson M. Genomic analysis identifies association of Fusobacterium with colorectal carcinoma. *Genome Res* 2012; **22**: 292-298 [PMID: 22009990 DOI: 10.1101/gr.126573.111]
58 **Ahn J**, Sinha R, Pei Z, Dominianni C, Wu J, Shi J, Goedert JJ, Hayes RB, Yang L. Human gut microbiome and risk for colorectal cancer. *J Natl Cancer Inst* 2013; **105**: 1907-1911 [PMID: 24316595 DOI: 10.1093/jnci/djt300]
59 **Hughes R**, Cross AJ, Pollock JR, Bingham S. Dose-dependent effect of dietary meat on endogenous colonic N-nitrosation. *Carcinogenesis* 2001; **22**: 199-202 [PMID: 11159760]
60 **Wollowski I**, Rechkemmer G, Pool-Zobel BL. Protective role of probiotics and prebiotics in colon cancer. *Am J Clin Nutr* 2001; **73**: 451S-455S [PMID: 11157356]
61 **Moore WE**, Moore LH. Intestinal floras of populations that have a high risk of colon cancer. *Appl Environ Microbiol* 1995; **61**: 3202-3207 [PMID: 7574628]
62 **James WPT**, Jackson-Leach R, Mhurchu CN, Kalamara E, Shayeghi M, Rigby NJ, Nishida C, Rodgers A. Overweight and obesity (high body mass index). Comparative quantification of health risks: global and regional burden of disease attribution to selected major risk factors volume 1. Geneva: World Health Organization, 2004: 497-596
63 **KD B**, Puhl RM. Weight bias; nature, consequences, and remedies. In: Fikkan J, Rothblum E. Weight bias in employment. Guilford Press, 2005
64 **Ezzati M**, Lopez AD, Rodgers A, Vander Hoorn S, Murray CJ. Selected major risk factors and global and regional burden of disease. *Lancet* 2002; **360**: 1347-1360 [PMID: 12423980]
65 **Turnbaugh PJ**, Ley RE, Mahowald MA, Magrini V, Mardis ER, Gordon JI. An obesity-associated gut microbiome with increased capacity for energy harvest. *Nature* 2006; **444**: 1027-1031 [PMID: 17183312]
66 **Bäckhed F**, Ley RE, Sonnenburg JL, Peterson DA, Gordon JI. Host-bacterial mutualism in the human intestine. *Science* 2005; **307**: 1915-1920 [PMID: 15790844 DOI: 10.1126/science.1104816]
67 **Bäckhed F**, Manchester JK, Semenkovich CF, Gordon JI. Mechanisms underlying the resistance to diet-induced obesity in germ-free mice. *Proc Natl Acad Sci USA* 2007; **104**: 979-984 [PMID: 17210919]
68 **Kalliomäki M**, Collado MC, Salminen S, Isolauri E. Early differences in fecal microbiota composition in children may predict overweight. *Am J Clin Nutr* 2008; **87**: 534-538 [PMID: 18326589]
69 **Turnbaugh PJ**, Hamady M, Yatsunenko T, Cantarel BL, Duncan A, Ley RE, Sogin ML, Jones WJ, Roe BA, Affourtit JP, Egholm M, Henrissat B, Heath AC, Knight R, Gordon JI. A core gut microbiome in obese and lean twins. *Nature* 2009; **457**: 480-484 [PMID: 19043404 DOI: 10.1038/nature07540]
70 **Spencer MD**, Hamp TJ, Reid RW, Fischer LM, Zeisel SH, Fodor AA. Association between composition of the human gastrointestinal microbiome and development of fatty liver with choline deficiency. *Gastroenterology* 2011; **140**: 976-986 [PMID: 21129376 DOI: 10.1053/j.gastro.2010.11.049]
71 **Karlsson CL**, Onnerfält J, Xu J, Molin G, Ahrné S, Thorngren-Jerneck K. The microbiota of the gut in preschool children with normal and excessive body weight. *Obesity* (Silver Spring) 2012; **20**: 2257-2261 [PMID: 22546742 DOI: 10.1038/oby.2012.110]
72 **Luoto R**, Kalliomäki M, Laitinen K, Delzenne NM, Cani PD, Salminen S, Isolauri E. Initial dietary and microbiological environments deviate in normal-weight compared to overweight children at 10 years of age. *J Pediatr Gastroenterol Nutr* 2011; **52**: 90-95 [PMID: 21150648 DOI: 10.1097/MPG.0b013e3181f3457f]
73 **Luoto R**, Kalliomäki M, Laitinen K, Isolauri E. The impact of perinatal probiotic intervention on the development of overweight and obesity: follow-up study from birth to 10 years. *Int J Obes* (Lond) 2010; **34**: 1531-1537 [PMID: 20231842 DOI: 10.1038/ijo.2010.50]
74 **Collado MC**, Isolauri E, Laitinen K, Salminen S. Distinct composition of gut microbiota during pregnancy in overweight and normal-weight women. *Am J Clin Nutr* 2008; **88**: 894-899 [PMID: 18842773]
75 **Furness JB**. Novel gut afferents: Intrinsic afferent neurons and intestinofugal neurons. *Auton Neurosci* 2006; **125**: 81-85 [PMID: 16476573]
76 **Collins SM**. Stress and the Gastrointestinal Tract IV. Modulation of intestinal inflammation by stress: basic mechanisms and clinical relevance. *Am J Physiol Gastrointest Liver Physiol* 2001; **280**: G315-G318 [PMID: 11171612]
77 **Wu JC**. Psychological Co-morbidity in Functional Gastrointestinal Disorders: Epidemiology, Mechanisms and Management. *J Neurogastroenterol Motil* 2012; **18**: 13-18 [PMID: 22323984 DOI: 10.5056/jnm.2012.18.1.13]
78 **Lyons V**, Fitzgerald M. Asperger (1906-1980) and Kanner (1894-1981), the two pioneers of autism. *J Autism Dev Disord* 2007; **37**: 2022-2023 [PMID: 17922179]
79 **Wolff S**. The history of autism. European Child and Adolescent *Psychiatry* 2004; **13**: 201 [DOI: 10.1007/s00787-004-0363-5]
80 **de Theije CG**, Wu J, da Silva SL, Kamphuis PJ, Garssen J, Korte SM, Kraneveld AD. Pathways underlying the gut-to-brain connection in autism spectrum disorders as future targets for disease management. *Eur J Pharmacol* 2011; **668** Suppl 1: S70-S80 [PMID: 21810417 DOI: 10.1016/j.ejphar.2011.07.013]

81 **Bolte ER**. Autism and Clostridium tetani. *Med Hypotheses* 1998; **51**: 133-144 [PMID: 9881820]

82 **Sandler RH**, Finegold SM, Bolte ER, Buchanan CP, Maxwell AP, Väisänen ML, Nelson MN, Wexler HM. Short-term benefit from oral vancomycin treatment of regressive-onset autism. *J Child Neurol* 2000; **15**: 429-435 [PMID: 10921511]

83 **MacFabe DF**, Cain DP, Rodriguez-Capote K, Franklin AE, Hoffman JE, Boon F, Taylor AR, Kavaliers M, Ossenkopp KP. Neurobiological effects of intraventricular propionic acid in rats: possible role of short chain fatty acids on the pathogenesis and characteristics of autism spectrum disorders. *Behav Brain Res* 2007; **176**: 149-169 [PMID: 16950524]

84 **Adams JB**, Johansen LJ, Powell LD, Quig D, Rubin RA. Gastrointestinal flora and gastrointestinal status in children with autism--comparisons to typical children and correlation with autism severity. *BMC Gastroenterol* 2011; **11**: 22 [PMID: 21410934 DOI: 10.1186/1471-230X-11-22]

85 **De Angelis M**, Piccolo M, Vannini L, Siragusa S, De Giacomo A, Serrazzanetti DI, Cristofori F, Guerzoni ME, Gobbetti M, Francavilla R. Fecal microbiota and metabolome of children with autism and pervasive developmental disorder not otherwise specified. *PLoS One* 2013; **8**: e76993 [PMID: 24130822 DOI: 10.1371/journal.pone.0076993]

86 **Finegold SM**, Dowd SE, Gontcharova V, Liu C, Henley KE, Wolcott RD, Youn E, Summanen PH, Granpeesheh D, Dixon D, Liu M, Molitoris DR, Green JA. Pyrosequencing study of fecal microflora of autistic and control children. *Anaerobe* 2010; **16**: 444-453 [PMID: 20603222 DOI: 10.1016/j.anaerobe.2010.06.008]

87 **Finegold SM**, Downes J, Summanen PH. Microbiology of regressive autism. *Anaerobe* 2012; **18**: 260-262 [PMID: 22202440 DOI: 10.1016/j.anaerobe.2011.12.018]

88 **Finegold SM**, Molitoris D, Song Y, Liu C, Vaisanen ML, Bolte E, McTeague M, Sandler R, Wexler H, Marlowe EM, Collins MD, Lawson PA, Summanen P, Baysallar M, Tomzynski TJ, Read E, Johnson E, Rolfe R, Nasir P, Shah H, Haake DA, Manning P, Kaul A. Gastrointestinal microflora studies in late-onset autism. *Clin Infect Dis* 2002; **35**: S6-S16 [PMID: 12173102]

89 **Parracho HM**, Bingham MO, Gibson GR, McCartney AL. Differences between the gut microflora of children with autistic spectrum disorders and that of healthy children. *J Med Microbiol* 2005; **54**: 987-991 [PMID: 16157555]

90 **Song Y**, Liu C, Molitoris DR, Tomzynski TJ, Lawson PA, Collins MD, Finegold SM. Clostridium bolteae sp. nov., isolated from human sources. *Syst Appl Microbiol* 2003; **26**: 84-89 [PMID: 12747414]

91 **Williams BL**, Hornig M, Parekh T, Lipkin WI. Application of novel PCR-based methods for detection, quantitation, and phylogenetic characterization of Sutterella species in intestinal biopsy samples from children with autism and gastrointestinal disturbances. *MBio* 2012; **3**: pii: e00261-11 [PMID: 22233678 DOI: 10.1128/mBio.00261-11]

92 **Gueimonde M**, Laitinen K, Salminen S, Isolauri E. Breast milk: a source of bifidobacteria for infant gut development and maturation? *Neonatology* 2007; **92**: 64-66 [PMID: 17596738]

93 **Martín R**, Heilig GH, Zoetendal EG, Smidt H, Rodríguez JM. Diversity of the Lactobacillus group in breast milk and vagina of healthy women and potential role in the colonization of the infant gut. *J Appl Microbiol* 2007; **103**: 2638-2644 [PMID: 18045446]

94 **Sinkiewicz G,** Nordström EA. 353 occurrence of lactobacillus reuteri, lactobacilli and bifidobacteria in human breast milk. *Pediatr Res* 2005; **58**: 415 [DOI: 10.1203/00006450-20050 8000-00382]

95 **Hsiao EY**, McBride SW, Hsien S, Sharon G, Hyde ER, McCue T, Codelli JA, Chow J, Reisman SE, Petrosino JF, Patterson PH, Mazmanian SK. Microbiota modulate behavioral and physiological abnormalities associated with neurodevelopmental disorders. *Cell* 2013; **155**: 1451-1463 [PMID: 24315484 DOI: 10.1016/j.cell.2013.11.024]

96 **Forsythe P**, Sudo N, Dinan T, Taylor VH, Bienenstock J. Mood and gut feelings. *Brain Behav Immun* 2010; **24**: 9-16 [PMID: 19481599 DOI: 10.1016/j.bbi.2009.05.058]

97 **Dethlefsen L**, Huse S, Sogin ML, Relman DA. The pervasive effects of an antibiotic on the human gut microbiota, as revealed by deep 16S rRNA sequencing. *PLoS Biol* 2008; **6**: e280 [PMID: 19018661 DOI: 10.1371/journal.pbio.0060280]

98 **Wang L**, Christophersen CT, Sorich MJ, Gerber JP, Angley MT, Conlon MA. Elevated fecal short chain fatty acid and ammonia concentrations in children with autism spectrum disorder. *Dig Dis Sci* 2012; **57**: 2096-2102 [PMID: 22535281 DOI: 10.1007/s10620-012-2167-7]

P- Reviewer: Balaban YH, Botaitis SC, Muguruma N, Rabago L, Zhang XC
S- Editor: Tian YL **L- Editor**: A **E- Editor**: Liu SQ

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com