Review Article

PGHN

Microbiome-Linked Crosstalk in the Gastrointestinal Exposome towards Host Health and Disease

Yuseok Moon[*,†,‡]

Laboratory of Mucosal Exposome and Biomodulation, Department of Biomedical Sciences, Pusan National University School of Medicine, Yangsan, †Research Institute for Basic Sciences and Medical Research Institute, Pusan National University, ‡Immunoregulatory Therapeutics Group in Brain Busan 21 Project, Busan, Korea

The gastrointestinal exposome represents the integration of all xenobiotic components and host-derived endogenous components affecting the host health, disease progression and ultimately clinical outcomes during the lifespan. The human gut microbiome as a dynamic exposome of commensalism continuously interacts with other exogenous exposome as well as host sentineling components including the immune and neuroendocrine circuit. The composition and diversity of the microbiome are established on the basis of the luminal environment (physical, chemical and biological exposome) and host surveillance at each part of the gastrointestinal lining. Whereas the chemical exposome derived from nutrients and other xenobiotics can influence the dynamics of microbiome community (the stability, diversity, or resilience), the microbiomes reciprocally alter the bioavailability and activities of the chemical exposome in the mucosa. In particular, xenobiotic metabolites by the gut microbial enzymes can be either beneficial or detrimental to the host health although xenobiotics can alter the composition and diversity of the gut microbiome. The integration of the mucosal crosstalk in the exposome determines the fate of microbiome community and host response to the etiologic factors of disease. Therefore, the network between microbiome and other mucosal exposome would provide new insights into the clinical intervention against the mucosal or systemic disorders via regulation of the gut-associated immunological, metabolic, or neuroendocrine system.

Key Words: Gastrointestinal exposome, Microbiota, Gastrointestinal immunity and inflammation, Xenobiotic metabolism

INTRODUCTION

Total human cells in the body (10^{13}) are outnumbered by bacterial cells as the human microbiome (10^{14}). This dominant player with the endogenous host factors can be influenced by foodborne factors including dietary components, infective agents and xenobiotic including drugs and toxins,

linked to diverse pathophysiological events including inflammation, carcinogenesis, metabolic syndromes, and neurological outcomes. The gastrointestinal mucosa shows typical microbiological and environmental features. From the proximal to the distal part of intestine, the oxygen levels are dramatically decreased, resulting in the dominancy of anaerobic microbes in the colon. Moreover, facultative players such as Bacterodetes burn out oxygen, attenuating the detrimental actions of oxygen species against the obligate anaerobes including commensal Clostria. There are two critical points for acidic environment in the human gut. One is the gastric cell-derived production of acids as a disinfectant, leading the drop in pH, but the pancreatic bicarbonate attenuate the acidity and the subsequent luminal fluid get more basic from the duodenum. The next drop in pH of the intestinal lumen is facilitated by outgrowing of fermentative microbes from the cecum, releasing out acidic organic metabolites such as short chain fatty acids (SCFAs). In response to oxygen tension and acidity, the composition of microbes can be differentially regulated at each segment of the gut lining. Along the dynamic features of fluid acidity and oxygen content in the gut lumen, nutritional components also affect the gut microbial diversity and stability via their acute and chronic actions. Since the simple sugars released form the carbohydrate degradation are easily consumed by the microbes in the proximal part of the gut, the lower lining of the gut are in short of the simple sugars and the remaining complex carbohydrates are utilized by fermenting anaerobes which dominate in the colon. Since the small intestinal lumen is generally more acidic environment with higher levels of oxygen, bile salts, and antimicrobial peptides than the colon lumen, simple sugar-favoring facultative anaerobes such as phyla Firmicutes (segmented filamentous bacteria [SFB] and Lactobacillaceae) and Proteobacteria (Enterobacteriaceae and *Helicobacter* spp.) can dominate in this proximal intestine. In contrast, the colon nutritional environment is favored by polysaccharide-utilizing anaerobes such as phyla Bacteroidetes, Actinobacteria (Bifidobacteriaceae), and

Firmicutes (Clostridia).

Moreover, nutrients and mucosal microbiomes are crucial modulators of gut sentinels including the mucosal immune systems and the intestinal neuroendocrine circuit. Foodborne factors can influence the composition and diversity of gut microorganisms, all of which impacts the immune and neuroendocrine responses in the gut via the various types of cytokines, hormones, and other messenger molecules. Moreover, the gastrointestinal immune sentineling signals are intimately linked with the neuroendocrine sentineling systems. Many of metabolic, inflammatory, and oncogenic disorders are due to the disruption of the two sentineling systems against nutrients and microbial community in the gut. The present review will address the features and networks of the gastrointestinal mucosal exposome to provide insights into the future intervention against mucosal diseases and mucosa-associated systemic diseases.

FEATURES OF STABILITY, DIVERSITY, FUNCTIONAL REDUNDANCY, AND RESILIENCE OF GUT MICROBIOME IN RESPONSE TO MUCOSAL EXPOSOME

The gastrointestinal exposome represents the integral of gut luminal exposure to both exogenous and endogenous factors in the host during the whole lifespan. From the birth, humans receive series of microbial population which collectively forms ecosystem of human microbiome and sometimes can be disturbed by both internal and external factors. The host interaction with microbiome is not a static, but rather dynamic with time. These mucosal disturbance may be stabilized, but which means the ecosystem reached the stable equilibrium states and any future stochastic disturbances can produce another stable state with dynamic changes in the community. The stable human microbiome can be classified into three enterotypes based on the stable distinct host–microbial nutritional symbiotic states characterized by a relatively high representation of Bacteroides, Prevotella or Ruminococcus [1,2]. Using

these enterotypes, microbiome-based nutritional or drug metabolism can be estimated and clinically useful to prevent idiosyncratic hypersensitivity to food and drugs, and metabolic activation-induced toxicity [3]. Moreover, nutritional recommendation could be individually selected based on personal enterotypes to control the metabolism-linked disorders such as hypercholesterolemia, diabetes and obesity [4].

In response to dietary mucosal exposome, resilience of microbiome can be developed. The degree of resilience is the amount of stress or perturbation that a system can tolerate the changes to a different equilibrium stable state [5]. The species diversity is crucial for maintaining conferring resilience since species-rich communities containing microorganisms efficiently utilizing the limiting resources are less susceptible to invasion by different species specialized to potentially use the limiting resource. In addition, functional diversity is also important to keep the microbiome resilience. Human gut-adapted bacteria are prone to show functional redundancy even though they are phylogenetically disparate [6]. For instance, in response to an X component, a previously rare X-metabolizing microbe can be abundant to replace the niche that had been dominated by a microorganism with higher aversion to X, which indicates the community keeps the stable condition with high resilience although phylogenetically typical groups are missing in response to some stressors.

The representative xenobiotic components in the mucosal exposome include drugs, nutrients and other adverse factors such as foodborne pathogens, biological toxins and other synthetic contaminants. The gastrointestinal exposome is the integration of the external components with all mucosal microbiome which function in both the gut physiology and pathology during the entire lifespan [7,8]. The homeostatic mucosal network would contribute to the stable equilibrium of the microbiome and host integrity. For instance, a high-fat diet (HFD) can change the dominancy and diversity of the intestinal microbiota, sometimes independent of status of host disease. HFD reduces the proportion of phylum Bacteroidetes and increases the proportions of phylum Proteobacteria [9]; whereas high-fiber containing food, such as important non-digestible plant carbohydrates, increases the proportion of Firmicutes bacteria [10]. In addition to the nutritional regulation, host-derived defense molecules can determine the characteristic microbiome profile. For example, some of gut microbes can utilize mucosal mucins and a microbial preference for the complex glycan of mucin can promote the growth of a number of mucin-degrading bacteria, which may facilitate microbial translocation to lamina propria and circulatory system [11]. The mucosal exposome-associated mucosal disruption can result in various types of human diseases and the following sections will address the mucosal exposome-disrupted or −promoted human health, based on dynamic gastrointestinal interactions between food components, the gut microbiota, and host responses. The crosstalk occurring in the microbiome-linked gastrointestinal exposome would provide new insight into disease progression and its intervention. Various types of mucosal diseases are associated with the impaired tolerance to gut commensal bacteria [12,13]. For example, patients with inflammatory bowel disease (IBD) are likely to have abnormal changes in gut microbial composition (dysbiosis). Technically through the automated ribosomal intergenic spacer analysis, terminal restriction fragment length polymorphisms, and denaturing gradient gel electrophoresis, the intestinal microbial diversity in IBD patients may be decreased [14,15]. In addition to the diversity, the richness index of the gut bacterial species is also reduced in the IBD patients. As a potent etiological factor of chronic colitis including IBD, exposure to ribosome-inactivating foodborne toxins (ribotoxins) such as trichothecene mycotoxins, ricin and shiga toxins has been known to cause severe intestinal inflammatory disorders [16]. Although the gut microbes can alter the binding and toxicity of the ribotoxins [17,18], the ribotoxins reciprocally can increase the intestinal composition of aerobic bacteria including aerobic mesophilic bacteria and the richness of gut microbiome in the animal model [19,20],

which is a similar pattern of microbial dysbiosis in gut of IBD patients.

GUT MICROBIOME–INDUCED META–BOLITES AND THEIR ACTIONS

Gut microbiota can interact with the chemical exposome in four ways. As described in the previous section, the chemical exposome can alter the composition, diversity and their biological activity of the gut microbiota. In particular, some of chemical xenobiotics can interfere with the metabolic activity of the microbiota-derived drug metabolism. Reciprocally, the gut microbiota can metabolize a variety of chemical xenobiotics directly upon ingestion in the gastrointestinal lumen or after the conjugated metabolites via enterohepatic circulation. Most of non-polar xenobiotics would be easily absorbed from the gut lumen and then transported to the liver for detoxification via the portal vein. The hepatic metabolic enzymes tends to oxidize the absorbed chemical xenobiotics, or catalyze the conjugation reactions with endogenous functional groups including glucuronic acid, sulfate, or glutathione. The hepatic metabolites can circulate or can be excreted in the bile and re-enter the intestinal lumen where the gut microbiota-mediated metabolism of the hepatic metabolites can take place. Some of gut microbiota produces extensive pools of enzymes including cytochrome p450 (CYP), catalyzing oxidative metabolism of foodborne components and oral medicines [21]. For instance, intestinal *Eubacterium aerofaciens*, *Desulfomonas pigra*, and *Streptomyces coelicolor* A3 isolated from human feces have CYP-like enzymes [22,23]. However, most xenobiotic metabolisms by gut microbiota have the preferences to the de-conjugation and reduction of the hepatic xenobiotic metabolites, ultimately producing non-polar metabolites of lower molecular weight, which are readily reabsorbed from the gut barrier into the circulation. Therefore, microbiota-mediated de-conjugation of hepatic conjugated metabolites may lead to regeneration of the original chemical xenobiotics or new metabolites with either higher or lower toxicity.

In the following sections, microbiota-mediated xenobiotic metabolism will be associated with modulation of gastrointestinal health or disorders such as inflammatory and oncogenic outcomes in the mucosa and circulation.

Short chain fatty acids

Dietary fibers are fermented into health-promoting components such as SCFAs by gut microbiota. Soluble elements of dietary fibers, such as pectin, gum, and mucilages, can be degraded into bioactive SCFAs, which are saturated aliphatic organic acids consisting of one to six carbons. Acetate (C2), propionate (C3), and butyrate (C4) are the most prevalent forms in the colon with a ratio of 60:20:20 (%) [24,25]. Most of SCFAs (95%) produced in the cecum and large intestine are readily absorbed by the gut epithelia [24]. In particular, the proximal colon is the principal site for the conversion of indigestible fibers to SCFAs by phylum Bacteroidetes such as butyrate-producing Bacteroides spp. [24] and thus the distal parts of the colon with increase of pH are dominated by populations of acetate- and propionate-producing Bacteroides-related spp. [26]. However, fermentation of bacterial proteins and amino acids still occurs in the more distal parts of the colon by the support of the secondary proteolytic fermenters, secreting potentially toxic metabolites such as amines, phenolic compounds, and volatile sulfur compounds [26]. Biochemically, SCFA can partially inhibit histone deacetylase (HDAC), which increases immunological tolerance and anti-inflammatory and anti-cancer responses [27-29]. Bacterial metabolite-sensing G protein coupled receptors (GPCRs) also play regulatory functions in gastrointestinal inflammation and metabolic syndromes by changing leptin production, adiposity, and insulin secretion [30]. In particular, SCFAs induce peptide secretion via GPCR activation on entero-endocrine cells (EECs), suggesting that the gut microbiota-neuronal axis can modulate some of GPCR-linked functions such as nutrient sensing and energy balance [31]. Moreover, prebiotic application alters the production of the gut microbial SCFA, resulting in gut peptide secretion from

EEC and subsequent host eating behavior [32]. For instance, prebiotics increase the abundance of *Bifido-bacterium* and *Lactobacillus*, as well as microbiota profiles skewing EEC differentiation and subsequently gut peptide production, ultimately increasing satiety response and decreasing energy intake, fat mass, and body weight. All of the information suggests the crucial regulation of food intake and maintenance of energy metabolism by microbiota and their metabolites including SCFAs [33-35].

Gut microbial metabolites as ligands for aryl hydrocarbon receptor

In addition to some flavonoids and indoles from plant-derived foodstuffs such as cruciferous vegetables, gut microbial metabolites such as pigment phenazins, nephtoquinon phthlocol, and dihydroxynaphthoic acid can activate aryl hydrocarbon receptor (AhR), a crucial nuclear receptor modulating expression of many genes that control immunity and inflammation [36]. Moreover, diet-derived tryptophan is metabolized by the microbiota (e.g., Lactobacilli) to indole-3-aldehyde, an AhR agonist. Intestinal indoleamine 2,3-dioxygenase can catalyze the conversion of tryptophan to kynurenine, another AhR ligand [37]. This AhR modulation by gut bacterial metabolites could be a co-evolutionary strategy between gut commensal bacteria and host immune system since ligand-activated AhR is closely involved in mucosal immune tolerance, leading to shaping of the microbial community through the actions of regulatory T cells and interleukin 22, which facilitate the host protection against excessive inflammation and microbial infection [38]. However, chronic AhR activation is not always beneficial since it can allows transformed tumor cells to evade from the immune-mediated attack, particularly at late stages of tumorigenesis [39,40]. Moreover, tryptophan metabolites, such as kynurenic acid and niacin, also interact with certain GPCRs as SCFAs do [30]. Bacterial metabolite-sensing GPCRs can be also involved in the regulatory action against gastrointestinal inflammation and metabolic syndromes. Taken together, microbiota metabolite-linked GPCRs,

HDACs, or AhR could be promising targets of clinical intervention against many mucosal inflammatory, metabolic or oncogenic diseases.

Gut microbiota-derived detrimental metabolites

By contrast with the beneficial effects, gut microbiota-mediated metabolism of chemical xenobiotics could result in harmful complications. For instance, gut microbial metabolism of the dietary phosphatidylcholine (PC), such as choline, lecithin, trimethylamine (TMA) N-oxide, and betaine, pose potent risk of causing cardiovascular diseases [41,42]. In addition to the PC, diet-derived L-carnitine can be metabolized into TMA by the gut microbiota [43]. TMA is further converted into TMA N-oxide (TMAO) by hepatic flavin monooxygenase or gut microbial enzymes. Along with TMA, TMAO is also an etiological factor of cardiovascular inflammatory disorders [36,41]. Mechanistically, treatment with TMA or TMAO increase the activated macrophage and endothelial injuries in the blood vessel.

Endogenous components can be transformed into detrimental metabolites by gut microbiota. For example, intestinal bacteria can convert the primary bile acids into the secondary bile acid metabolites such as deoxycholic acid and lithocholic acid which cause oxidative and nitrosative stress, resulting in genetic damages of enterocytes and gut inflammatory lesions including high levels of flat adenoma lesions and hyperplasia of Peyer's patches. Frequent and chronic mucosal exposure to the secondary bile acids thus can increase the genomic instability, chemoresistance and tumor progression [44,45].

CONCLUSION

The composition and diversity of the microbiome are specified, depending on the mucosal exposome and host sentineling systems. The chemical exposome derived from nutrients and other xenobiotics may alter the microbiome community in terms of the stability, diversity, or functional redundancy. Reciprocally, the gut microbiomes provides
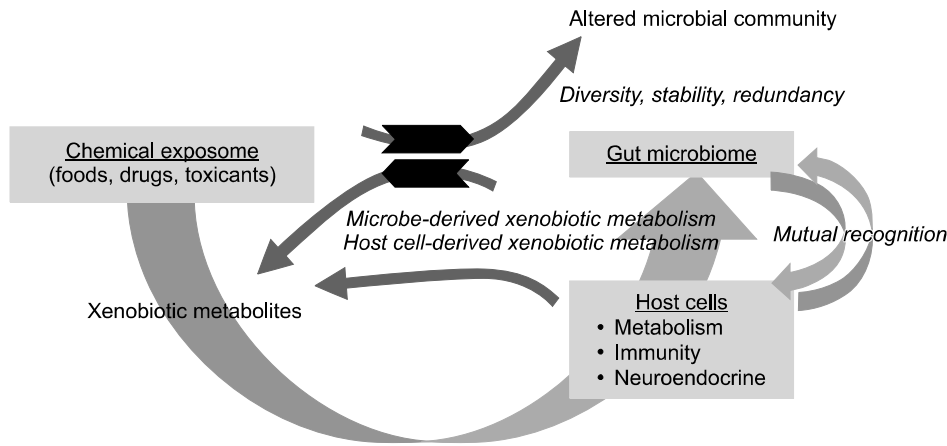
Fig. 1. Schematic networks of gastrointestinal niche. Mucosal xenobiotics are converted into beneficial or harmful metabolites by both host cells and gut microbes, which reciprocally influces the microbial community and host cell integrity. Gut microbes are continuously interplaying with the host sentinels such as immune and neuroendocrine systems.

critical sources for xenobiotic metabolism of the chemical exposome in the mucosa and hepatic metabolites from the enterohepatic circulation. Of note, xenobiotic metabolites by the gut microbial enzymes can be either beneficial or detrimental to the host health. Total integration of the crosstalk in the mucosal exposome would determines the fate of microbiome community and host response to the xenobiotics via regulation of the sentineling systems including immune and neuroendocrine tissues (Fig. 1). As the clinical implications, the disease progress can be assessed by reading out the mucosal biomarkers from the network between exposome and host. Moreover, the preventive or therapeutic intervention against the mucosal or systemic disorders may be performed by targeting at the crosstalk between microbiome and other mucosal exposome under the host sentineling system.

ACKNOWLEDGEMENTS

REFERENCES

1. Arumugam M, Raes J, Pelletier E, Le Paslier D, Yamada T, Mende DR, et al. Enterotypes of the human gut microbiome. Nature 2011;473:174-80.
2. Koren O, Knights D, Gonzalez A, Waldron L, Segata N, Knight R, et al. A guide to enterotypes across the human body: meta-analysis of microbial community structures in human microbiome datasets. PLoS Comput Biol 2013;9:e1002863.
3. Raymond F, Ouameur AA, Déraspe M, Iqbal N, Gingras H, Dridi B, et al. The initial state of the human gut microbiome determines its reshaping by antibiotics. ISME J 2016;10:707-20.
4. Kang C, Zhang Y, Zhu X, Liu K, Wang X, Chen M, et al. Healthy subjects differentially respond to dietary capsaicin correlating with specific gut enterotypes. J Clin Endocrinol Metab 2016;101:4681-9.
5. Gibson MK, Pesesky MW, Dantas G. The yin and yang of bacterial resilience in the human gut microbiota. J Mol Biol 2014;426:3866-76.
6. Lozupone CA, Stombaugh JI, Gordon JI, Jansson JK, Knight R. Diversity, stability and resilience of the human gut microbiota. Nature 2012;489:220-30.
7. Fiocchi C. Towards a 'cure' for IBD. Dig Dis 2012;30: 428-33.
8. Fiocchi C. Integrating omics: the future of IBD? Dig Dis 2014;32 Suppl 1:96-102.
9. Hildebrandt MA, Hoffmann C, Sherrill-Mix SA, Keilbaugh SA, Hamady M, Chen YY, et al. High-fat diet determines the composition of the murine gut microbiome independently of obesity. Gastroenterology 2009;137:1716-24.e1-2.
10. Walker AW, Ince J, Duncan SH, Webster LM, Holtrop G, Ze X, et al. Dominant and diet-responsive groups of bacteria within the human colonic microbiota. ISME J 2011;5:220-30.
11. Donaldson GP, Lee SM, Mazmanian SK. Gut bio-

geography of the bacterial microbiota. Nat Rev Microbiol 2016;14:20-32.

12. Fava F, Danese S. Intestinal microbiota in inflammatory bowel disease: friend of foe? World J Gastroenterol 2011;17:557-66.

13. Scharl M, Rogler G. Microbial sensing by the intestinal epithelium in the pathogenesis of inflammatory bowel disease. Int J Inflam 2010;2010:671258.

14. Scanlan PD, Shanahan F, O'Mahony C, Marchesi JR. Culture-independent analyses of temporal variation of the dominant fecal microbiota and targeted bacterial subgroups in Crohn's disease. J Clin Microbiol 2006; 44:3980-8.

15. Sepehri S, Kotlowski R, Bernstein CN, Krause DO. Microbial diversity of inflamed and noninflamed gut biopsy tissues in inflammatory bowel disease. Inflamm Bowel Dis 2007;13:675-83.

16. Abreu MT, Arnold ET, Thomas LS, Gonsky R, Zhou Y, Hu B, et al. TLR4 and MD-2 expression is regulated by immune-mediated signals in human intestinal epithelial cells. J Biol Chem 2002;277:20431-7.

17. Awad WA, Ghareeb K, Bohm J, Zentek J. Decontamination and detoxification strategies for the Fusarium mycotoxin deoxynivalenol in animal feed and the effectiveness of microbial biodegradation. Food Addit Contam Part A Chem Anal Control Expo Risk Assess 2010; 27:510-20.

18. Yu H, Zhou T, Gong J, Young C, Su X, Li XZ, et al. Isolation of deoxynivalenol-transforming bacteria from the chicken intestines using the approach of PCR-DGGE guided microbial selection. BMC Microbiol 2010;10:182.

19. Tenk I, Fodor E, Szathmáry C. The effect of pure Fusarium toxins (T-2, F-2, DAS) on the microflora of the gut and on plasma glucocorticoid levels in rat and swine. Zentralbl Bakteriol Mikrobiol Hyg A 1982;252:384-93.

20. Waché YJ, Valat C, Postollec G, Bougeard S, Burel C, Oswald IP, et al. Impact of deoxynivalenol on the intestinal microflora of pigs. Int J Mol Sci 2009;10:1-17.

21. Bezirtzoglou EE. Intestinal cytochromes P450 regulating the intestinal microbiota and its probiotic profile. Microb Ecol Health Dis 2012;23:10.3402/mehd.v23io. 18370.

22. Lei L, Waterman MR, Fulco AJ, Kelly SL, Lamb DC. Availability of specific reductases controls the temporal activity of the cytochrome P450 complement of Streptomyces coelicolor A3(2). Proc Natl Acad Sci U S A 2004; 101:494-9.

23. Sperry JF, Wilkins TD. Presence of cytochrome c in Desulfomonas pigra. J Bacteriol 1977;129:554-5.

24. den Besten G, van Eunen K, Groen AK, Venema K, Reijngoud DJ, Bakker BM. The role of short-chain fatty acids in the interplay between diet, gut microbiota, and host energy metabolism. J Lipid Res 2013;54:2325-40.

25. Hamer HM, Jonkers D, Venema K, Vanhoutvin S, Troost FJ, Brummer RJ. Review article: the role of butyrate on colonic function. Aliment Pharmacol Ther 2008;27:104-19.

26. Macfarlane GT, Macfarlane S. Fermentation in the human large intestine: its physiologic consequences and the potential contribution of prebiotics. J Clin Gastroenterol 2011;45 Suppl:S120-7.

27. Schilderink R, Verseijden C, de Jonge WJ. Dietary inhibitors of histone deacetylases in intestinal immunity and homeostasis. Front Immunol 2013;4:226.

28. Schilderink R, Verseijden C, Seppen J, Muncan V, van den Brink GR, Lambers TT, et al. The SCFA butyrate stimulates the epithelial production of retinoic acid via inhibition of epithelial HDAC. Am J Physiol Gastrointest Liver Physiol 2016;310:G1138-46.

29. Tong X, Yin L, Giardina C. Butyrate suppresses Cox-2 activation in colon cancer cells through HDAC inhibition. Biochem Biophys Res Commun 2004;317: 463-71.

30. Thorburn AN, Macia L, Mackay CR. Diet, metabolites, and "western-lifestyle" inflammatory diseases. Immunity 2014;40:833-42.

31. Bercik P, Denou E, Collins J, Jackson W, Lu J, Jury J, et al. The intestinal microbiota affect central levels of brain-derived neurotropic factor and behavior in mice. Gastroenterology 2011;141:599-609, 609.e1-3.

32. Duca FA, Lam TK. Gut microbiota, nutrient sensing and energy balance. Diabetes Obes Metab 2014;16 Suppl 1:68-76.

33. Paul HA, Bomhof MR, Vogel HJ, Reimer RA. Diet-induced changes in maternal gut microbiota and metabolomic profiles influence programming of offspring obesity risk in rats. Sci Rep 2016;6:20683.

34. Reid DT, Eller LK, Nettleton JE, Reimer RA. Postnatal prebiotic fibre intake mitigates some detrimental metabolic outcomes of early overnutrition in rats. Eur J Nutr 2016;55:2399-409.

35. Yang J, Summanen PH, Henning SM, Hsu M, Lam H, Huang J, et al. Xylooligosaccharide supplementation alters gut bacteria in both healthy and prediabetic adults: a pilot study. Front Physiol 2015;6:216.

36. Tilg H, Moschen AR. Food, immunity, and the microbiome. Gastroenterology 2015;148:1107-19.

37. Zelante T, Iannitti RG, Cunha C, De Luca A, Giovannini G, Pieraccini G, et al. Tryptophan catabolites from microbiota engage aryl hydrocarbon receptor and balance mucosal reactivity via interleukin-22. Immunity

2013;39:372-85.

38. Ikuta T, Kurosumi M, Yatsuoka T, Nishimura Y. Tissue distribution of aryl hydrocarbon receptor in the intestine: Implication of putative roles in tumor suppression. Exp Cell Res 2016;343:126-34.

39. Esser C, Rannug A. The aryl hydrocarbon receptor in barrier organ physiology, immunology, and toxicology. Pharmacol Rev 2015;67:259-79.

40. Murray IA, Patterson AD, Perdew GH. Aryl hydrocarbon receptor ligands in cancer: friend and foe. Nat Rev Cancer 2014;14:801-14.

41. Hartiala J, Bennett BJ, Tang WH, Wang Z, Stewart AF, Roberts R, et al. Comparative genome-wide association studies in mice and humans for trimethylamine N-oxide, a proatherogenic metabolite of choline and L-carnitine. Arterioscler Thromb Vasc Biol 2014;34: 1307-13.

42. Wang Z, Klipfell E, Bennett BJ, Koeth R, Levison BS, Dugar B, et al. Gut flora metabolism of phosphatidylcholine promotes cardiovascular disease. Nature 2011;472:57-63.

43. Koeth RA, Wang Z, Levison BS, Buffa JA, Org E, Sheehy BT, et al. Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis. Nat Med 2013;19:576-85.

44. Bernstein C, Holubec H, Bhattacharyya AK, Nguyen H, Payne CM, Zaitlin B, et al. Carcinogenicity of deoxycholate, a secondary bile acid. Arch Toxicol 2011;85: 863-71.

45. Saracut C, Molnar C, Russu C, Todoran N, Vlase L, Turdean S, et al. Secondary bile acids effects in colon pathology. Experimental mice study. Acta Cir Bras 2015;30:624-31.