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EDITORIAL

Gut microbiomes and their metabolites shape human and animal health

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The host genetic background, complex surrounding environments, and gut microbiome are very closely linked to human and animal health and disease. Although significant correlations between gut microbiota and human and animal health have been revealed, the specific roles of each gut bacterium in shaping human and animal health and disease remain unclear. However, recent omics-based studies using experimental animals and surveys of gut microbiota from unhealthy humans have provided insights into the relationships among microbial community, their metabolites, and human and animal health. This editorial introduces six review papers that provide new discoveries of disease-associated microbiomes and suggest possible microbiome-based therapeutic approaches to human disease.

Keywords: immunity, probiotics, disease, symbiosis, gut, rumen

The human gut microbiome comprises all the genetic material within a microbiota, including bacteria, archaea, viruses, and fungi in the human intestines. Dietary history, environmental conditions, and the host genetic background are all connected to the microbial compositions of human and animal guts, which determine the digestion process, immune responses, and allergic reactions. Species-level correlations with human ischemic stroke and phylum-level correlation with hypertension have been suggested; however, no clear mechanism to elucidate these relationships has been provided (Yamashiro *et al*., 2017). Although many studies have revealed interesting correlations between microbial community shifts and the health or disease of experimental animals, specific disease-related microbial community signatures and actual causality have not been clearly established. Microbial metabolites in the intestine, especially simple organic acids like acetate, propionate, and butyrate, appear to be associated with the increase and/or decrease of a specific group of bacterial genera. Reduction of the butyrate-producing genus *Roseburia* might be linked to atherosclerosis (Tang *et al*., 2017). In this special issue, Sittipo *et al*. (2018) review how changes of the intestinal microbiota and immune system affect metabolic diseases, such as obesity and diabetes. Five bacterial phyla have been reported to be dominant in the human intestinal microbiota: *Firmicutes*, *Bacteroidetes*, *Actinobacteria*, *Proteobacteria*, and *Verrucomicrobia*. *Bacteroidetes* and *Firmicutes* phyla occupy 70–90% of the total healthy human gut microbiota. With regard to obesity and type 2 diabetes (T2D), the build-up of members of the phylum *Firmicutes*, such as *Ruminococcus*, *Clostridium*, and *Lactobacillus*, and decrease in the numbers of the phylum *Bacteroidetes*, including *Bacteroides*, *Prevotella*, and *Xylanibacter*, are welldocumented (Ley *et al*., 2006; Turnbaugh *et al*., 2006). Obesity-associated gut *Firmicutes* presumably have more capacity to harvest energy from the diet, which leads to an increase of total body fat (Turnbaugh *et al*., 2006). Damaging intestinal epithelial barriers increases bacterial lipopolysaccharide infiltration. This bacterial disruption of the intestinal epithelial barrier is considered a possible mechanism to explain how high fat diet (HFD) induced microbial dysbiosis activates the immune response and insulin resistance (Ding *et al*., 2010). Distinct subsets of innate lymphoid cells (ILCs) are tightly linked to different types of metabolic diseases, such as obesity, insulin resistance, and T2D. Group 2 ILCs (ILC2s) control obesity by promoting metabolically active brown adipocytes. Depletion of ILC2s in HFD-fed mice and in obese mice has been observed (Klose and Artis, 2016). The gut microbiome influences the development and sustenance of ILCs subsets. Microbial dysbiosis produces different microbial metabolites and damages intestinal barrier integrity, which changes the production of adipose tissue macrophages (ATM), neutrophils, $CD8^+$ cells, and T helper type 2 (Th2) cells. Modulation of these immune components results in obesity, inflammation, and insulin resistance.

Park and Eberl (2018) highlight cellular and molecular mechanisms of microbiota-specific regulatory T cells (Tregs) and Th17 cells, which are linked to antimicrobial type 3 immunity. Type 3 immunity is essential to protect the body against extracellular bacteria and fungi. By contrast, other cell-mediated effector immunities, Type 1 and 2, are responsible for autoimmune diseases and allergic responses, respectively (van de Pavert *et al*., 2014). Type 3 immunity is mediated by retinoic acid-related orphan receptor γt^+ ($ROR\gamma t^+$)-controlled ILC3s and Th17 cells, which are associated with the production of mononuclear phagocytes, the recruitment of neutrophils, and the induction of epithelial antimicrobial responses. The gut microbiota produces short-

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chain fatty acids (SCFAs), including acetate, propionate, and butyrate, by fermenting dietary fiber, which triggers the expression of RALDH1 (a cell specific retinaldehyde dehydrogenase). *Clostridium* and *Bacteroides* species are the major producers of SCFAs in the intestine. The RALDHs generate retinoic acid (RA) by hydrolyzing retinaldehyde, a metabolite of host-produced vitamin A. RA is a signaling molecule that promotes the generation of RORγt^{+}-expressing Tregs over Th17 cells production (Arpaia *et al*., 2013). The balance between Tregs and Th17 cells regulated by RA is important for type 3 immunity. Other reports also suggested that tryptophan metabolites produced by *Lactobacillus* species modulate the activation of Th17 cells and group 3 ILCs (ILC3s) in the small intestine. Interestingly, IL-1β and IL-23, produced by dendritic cells (DCs) and macrophages, induce the generation of Th17 cells and ILC3s that are also under the control of RORγt^{+}. The dynamic cross-regulation of type 1, 2, and 3 responses and immune homeostasis, mean that further research is necessary to understand the interaction between immune responses and gut microbiota. However, it has been clearly shown that gut microbiota-induced type 3 immunity regulates type 2 responses, thus allergic inflammation at mucosal surfaces could be prevented.

There is an emerging understanding of the crosstalk between the gut environment and brain activity by gut microbial metabolites, such as gamma-aminobutyric acid (GABA), serotonin, and histamine; thus, alteration in gut microbial activity affects animal brain function and behavior (Bravo *et al.,* 2011, 2012). In this special issue, Kim *et al.* (2018) summarize the current status of these gut microbiota-brain interactions. Many studies have reported strong correlations between a variety of neurological diseases (e.g., multiple sclerosis, autism spectrum disorder (ASD), and Alzheimer's disease (AD)) and gut microbial composition changes and revealed an imbalance of the *Bacteroidetes* and *Firmicutes* ratio in neurological diseases. The actual mechanisms that explain these relationships are not fully developed; however, it has become obvious that gut microbiota can stimulate immune systems and microbially produced neuroactive compounds can affect brain function through the enteric nerve system (ENS). The ENS interacts with the autonomic nervous system (ANS) and the central nervous system (CNS) via neurotransmitters (adrenaline, noradrenaline, and acetylcholine), and many neurological diseases are accompanied by gut symptoms (e.g., constipation, diarrhea, and abdominal pain); thus, the gut environment appears to be connected to all nervous systems (Grenham *et al*., 2011). Many well-known gut bacteria produce neuroactive compounds; e.g., *Lactobacillus* and *Bifidobacterium* produce GABA; *Escherichia, Bacillus*, and *Saccharomyces* species produce norepinephrine; and *Lactococcus*, *Lactobacillus*, and *Serratia* produce dopamine. SCFAs interact directly or indirectly with the nervous system. Nervous system-controlled gut functions, such as gastrointestinal mobility, secretion of mucus, and epithelial permeability can also change the gut environment, which affect the composition of the gut microbial community. Patients with ASD have reductions in *Bacteroides* and increased levels of *Firmicutes* and *Clostridium* species. Interestingly, a recent study suggested that alterations in gut microbiota might contribute to amyloid deposition in AD mouse models (Harach *et al*., 2017). Further information must be accumulated to clarify the mechanisms of this brain-gut axis communication.

Replacing the microbial community in the patient gut with a microbiota from a healthy adult might be a future direction to treat some infectious diseases and neural disorders (Aron-Wisnewsky and Clement, 2016). Cho and Chinnapen (2018), in this issue, bring our attention to new therapeutic approaches using fecal microbial transplantation (FMT). Current knowledge concerning the gut microbiota and human health is insufficient; therefore, many clinicians overlook the role of the gut microbiota and overuse antibiotics, which leads to a reduction in the microbial diversity of the human gut (Lopez *et al*., 2014). *Clostridium difficile* colonizes the large intestine and causes a number of illnesses, including diarrhea, colitis, and sepsis. *Clostridium difficile* infection (CDI) most commonly affects people who have recently been treated with antibiotics. While continued antibiotic therapy was the treatment choice for CDI, frequently, it could not achieve a 100% cure of CDI. However, FMT treatment by restoring gut microbiota has been used to treat CDI successfully. FMT trials to treat inflammatory bowel disease (IBD) have been also reported. However, long-term monitoring of CDI and IBD using FMT are required to establish these FMT therapies, because host genetic differences might reduce the efficacy of FMT treatment. In the future, engineering targeted microbiomes and personalized FMT could be developed to treat many gut-associated diseases, after determining "who is doing what" in the gut microbiota. IBD resulting from genetic susceptibility, infection, western dietary habits, and administration of antibiotics could be treated using "microbiota therapies." In this special issue, Eom *et al.* (2018) introduce these new microbiota therapies to remedy gut dysbiosis, which are more effective and safer than conventional chemotherapies using medications such as corticosteroids, 5-aminosalicylates, and antibiotics. Although the pathogenesis of IBD is not completely understood, abnormal immune responses by decreasing Tregs and intestinal microbial shifts that reduce "healthy" gut microbiota could be associated with IBD. Eliminating butyrate-producing, mucindegrading commensal bacteria using antibiotics increased the numbers of antibiotic-resistant proinflammatory pathogenic bacteria, such as *Salmonella enterica* serotype Typhimurium and *Clostridium difficile* (Ng *et al*., 2013).

In this special issue, Dr. Suen's group focus on the *Ruminococcus* genus, which is commonly found in the rumen of animals, but is also present in non-ruminant animals, including humans (La Reau and Suen, 2018). In herbivorous ruminants, the gut microbiota including *Ruminococcus* genus is very important to degrade dietary cellulosic biomass into nutritive short-chain fatty acids. *Ruminococcus* species are essential for the survival of such rumen animals. Little is known about roles of non-cellulolytic *Ruminococcus* species in the degradation several di- and tri-saccharides present in all vegetables, fruit, and whole grains. *Ruminococcus* species are consistently present in the healthy human gut; therefore, possible roles in maintaining a healthy human gut environment are suggested. Large-scale genomic analysis for the taxonomic classification of *Ruminococcus* species led to the bacterial genus called "*Blautia*," formerly assigned to *Rumi-*

nococcus genus, being reclassified (La Reau *et al.,* 2016). This *Blautia* species occupies up to 16% of the microbiota of the human gastrointestinal tract and a significant reduction of *Blautia* species was observed in the elderly or patients with colorectal cancer. The most recent isolate from the human colon, *Ruminococcus bicirculans*, is non-cellulolytic, but can utilize specific hemicelluloses, such as barley beta-glucan, (1,4)-beta-D-mannan, and xyloglucan. *R. bicirculans* can produce acetate, ethanol, and formate by fermenting glucose, cellobiose, and soluble starch (Wegmann *et al.*, 2013). Human and animal gut environments harbor many minor groups whose roles in the gut environment are often neglected. Metabolic commensalisms, quorum sensing and quenching, syntrophic relationships, and production of known signaling molecules might occur among these minor groups and the dominant groups in the gut community. Further research on these issues is required to gain a complete picture of microbial functions in human and animal gut ecosystems.

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