Insights into host-microbe interaction: What can we do for the swine industry?

Lijuan Fan, Bingnan Liu, Ziyi Han, Wenkai Ren*

State Key Laboratory for Conservation and Utilization of Subtropical Agro-bioresources, Guangdong Laboratory of Lingnan Modern Agriculture, National Engineering Research Center for Breeding Swine Industry, Guangdong Provincial Key Laboratory of Animal Nutrition Control, College of Animal Science, South China Agricultural University, Guangzhou, 510642, China

Article info

Article history:
Received 28 July 2020
Received in revised form 13 October 2020
Accepted 16 October 2020
Available online 1 December 2020

Keywords:
Gut microbiota
Microbiota-gut-brain axis
Pig
Short-chain fatty acid
Tryptophan

Abstract

Recent discoveries have underscored the cross-talk between intestinal microbes and their hosts. Notably, intestinal microbiota impacts the development, physiological function and social behavior of hosts. This influence usually revolves around the microbiota-gut-brain axis (MGBA). In this review, we firstly outline the impacts of the host on colonization of intestinal microorganisms, and then highlight the influence of intestinal microbiota on hosts focusing on short-chain fatty acid (SCFA) and tryptophan metabolite-mediated MGBA. We also discuss the intervention of intestinal microbial metabolism by dietary supplements, which may provide new strategies for improving the welfare and production of pigs. Overall, we summarize a state-of-the-art theory that gut microbiome affects brain functions via metabolites from dietary macronutrients.

© 2021, Chinese Association of Animal Science and Veterinary Medicine. Production and hosting by Elsevier B.V. on behalf of KeAi Communications Co., Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Introduction

As an active player in host physiology, intestinal microbiota affects functions of the intestine and surrounding organs. Notably, through host-microbe dialogues, especially along the microbiota-gut-brain axis (MGBA), gut microbiome is involved in brain function and behavior through microbial metabolites (Gheorghe et al., 2019). For example, short-chain fatty acids (SCFA) fermented from dietary fiber in the colon directly or indirectly regulate brain function owing to their properties of neuroactivity and their impacts on cellular signaling pathways (Clarke et al., 2014; Stilling et al., 2016). Another example in the lexicon of host-microbial cross-talk is tryptophan because of the important physiological implications of microbial metabolism of tryptophan both in the gut and brain (Lee et al., 2015; Roager and Licht, 2018). As meat quality and product safety are the priority of the swine industry, the health and welfare of pigs are of universal importance for all swine producers (Lyte and Lyte, 2019). Interestingly, a stable and diverse flora structure is essential for the health and welfare of pigs. Here, with especial focusing on the information from pigs, we reviewed the establishment of intestinal microbes and their effects on hosts, highlighting dietary fiber and tryptophan metabolite-mediated MGBA. We propose a strategy to modify the microbiome through dietary intervention to enhance growth performance and well-being of pigs.

2. Variations in gut microbiota: factors from the host

Gut microbiota performs various functions in hosts, including nutrient metabolism, immunomodulation and protection against pathogens. Intestinal flora begins to colonize early in life, and its composition and distribution has a strong spatiotemporal specificity. In adulthood, the symbiotic core microbiota remains relatively stable, but differs between individuals. Although it is difficult to define the optimal composition of gut microbiota, the balance of host-microorganism is essential for metabolic and immune functions and prevention of intestinal diseases.
2.1. Physiological stage

Mammals were traditionally regarded as sterile during the fetal period, which has been questioned over recent years (Perez-Munoz et al., 2017). Analysis of meconium samples collected within 6 h after farrowing indicates that microbiome acquisition likely begins in utero, and meconium microbiome is likely to be vertically transmitted from the sows (Wang et al., 2019b). Another compelling study also provides evidence of bacterial colonization during the human fetal period (Collado and Segata, 2020). Although these studies provide evidence of the origin of intestinal microbiome, whether mammals are germ-free in fetal period is in debate, and the biological impact of intra-uterine microbial colonization on host development remains to be uncovered.

In contrast to the situation in the fetal period, it is widely accepted that gut microbe colonizes in neonates in an orderly manner after they are exposed to a wide variety of microorganisms (Von Mutius, 2017). Aerobic and facultative anaerobes such as Enterobacter, Enterococcus and Staphylococcus are first colonized in the intestine (Li et al., 2018; Huang et al., 2019). With the consumption of oxygen, the micro-environment of the gut gradually changes into an anaerobic state, which provides unique conditions for the colonization of specific anaerobes (Heinritz et al., 2013). During lactation, Lactobacillus and Streptococcus are dominant in the small intestine of piglets, but the intestinal environment changes abruptly after weaning, resulting in reconstruction of the microflora. For example, there is a clear difference in the α diversity of gut microbiota during weaning, and the α diversity increases even further after feeding a plant diet (Frese et al., 2015).

Besides diversity, there is a significant alteration in the fecal microbiota composition during weaning. Gut microbial communities include Firmicutes, Bacteroidetes, Proteobacteria, Spirochaetes and Tenericutes at the phylum level, which are 54.00%, 38.70%, 4.20%, 0.70% and 0.20%, respectively, at the pre-weaning period, and are 35.80%, 59.60%, 1.00%, 2.00% and 1.00%, respectively, at the post-weaning period (Pajarillo et al., 2014). In each situation, and even in growing-finishing pigs, the most abundant phyla are Firmicutes and Bacteroidetes, which account for more than 90% of the community (Kim et al., 2012; Kim and Isaacson, 2015). At the family level, relative abundances of Bacteroidaceae and Enterobacteriaceae decline gradually, but Veillonellaceae, Prevotellaceae, Lactobacillaceae and Ruminococcaceae increase in weaned piglets (Alain et al., 2014). At the genus level, weaning is associated with the reduction in Bacteroides, and increases in Lactobacillus and Prevotella (Guevarra et al., 2018). The possible reason is that Bacteroides use the monosaccharides and oligosaccharides in breast milk, and Prevotella degrades plant poly-saccharides in plant diets (Lamendella et al., 2011). After weaning, the changes of intestinal microflora continue until the market (Wang et al., 2019b). Collectively, the intestinal tract of weanling pigs, the most abundant genera of the Clostridiales, Bacilli, and Enterobacteriaceae family (17.10%) are the most abundant genera in the distal ileum. In the colon, the most dominant genus is Prevotella, representing 40.90% and 34.99% in the proximal and distal parts respectively (Zhang et al., 2018).

Owing to the rapid transformation of luminal contents and presence of digestion enzymes, the proximal small intestine is not suitable for bacterial colonization (Donaldson et al., 2016). Thus, there are relatively low numbers of bacteria, and the most abundant genera are Lactobacillus (45.79% and 36.75%, respectively) and Clostridium (25.64% and 29.67%, respectively) in the duodenum and jejunum. Bacterial growth in the distal ileum is possible owing to the neutral pH value, reduced oxygen availability, and lowered concentrations of compounds that challenge microbial growth. Streptococcus (17.73%) and the unspecified genera of the Clostridiales family (17.10%) are the most abundant genera in the ileum. In the colon, the most dominant genus is Prevotella, representing 40.90% and 34.99% in the proximal and distal parts respectively (Zhang et al., 2018).

Differences in microbial distribution are not only reflected in the longitudinal structure of the digestive tract, but in the direction of axial (Zhang et al., 2018). This is due to the response of microbial populations to different physicochemical conditions (Stearns et al., 2011). For example, an oxygen-abundant micro-environment is created in mucosa because of the diffusion of oxygen from the epithelial capillary to intestinal mucosa (Albenberg et al., 2014), thus, microaerophilic Helicobacteraceae and Campylobacteraceae are enriched, whereas obligate anaerobic bacteria from Prevotellaceae, Lachnospiraceae, Ruminococcaceae, and Veillonellaceae are abundant in the lumen of the cecum (Kelly et al., 2017; Zhang et al., 2018). Although it is accepted that intestinal microbes have the characteristics of compartmentalization in composition and function, there are various unanswered questions. For example, it is interesting to know whether the flora colonized in different ecological niches communicate and interact with each other.

2.2. Intestinal environment

The intestinal environment is one of the strongest determining factors for microbial colonization (Parker et al., 2018). The gut tract is composed of a series of connected specialized segments with certain amount of physiological pressures that affect bacterial colonization. Microbial communities of different niches of swine intestine have spatial heterogeneity (Looff et al., 2014; Donaldson et al., 2016) due to local environmental variations (Espey, 2013; Tropini et al., 2017; Zhang et al., 2018).

Owing to the rapid transformation of luminal contents and presence of digestion enzymes, the proximal small intestine is not suitable for bacterial colonization (Donaldson et al., 2016). Thus, there are relatively low numbers of bacteria, and the most abundant genera are Lactobacillus (45.79% and 36.75%, respectively) and Clostridium (25.64% and 29.67%, respectively) in the duodenum and jejunum. Bacterial growth in the distal ileum is possible owing to the neutral pH value, reduced oxygen availability, and lowered concentrations of compounds that challenge microbial growth. Streptococcus (17.73%) and the unspecified genera of the Clostridiales family (17.10%) are the most abundant genera in the ileum. In the colon, the most dominant genus is Prevotella, representing 40.90% and 34.99% in the proximal and distal parts respectively (Zhang et al., 2018).

Differences in microbial distribution are not only reflected in the longitudinal structure of the digestive tract, but in the direction of axial (Zhang et al., 2018). This is due to the response of microbial populations to different physicochemical conditions (Stearns et al., 2011). For example, an oxygen-abundant micro-environment is created in mucosa because of the diffusion of oxygen from the epithelial capillary to intestinal mucosa (Albenberg et al., 2014), thus, microaerophilic Helicobacteraceae and Campylobacteraceae are enriched, whereas obligate anaerobic bacteria from Prevotellaceae, Lachnospiraceae, Ruminococcaceae, and Veillonellaceae are abundant in the lumen of the cecum (Kelly et al., 2017; Zhang et al., 2018). Although it is accepted that intestinal microbes have the characteristics of compartmentalization in composition and function, there are various unanswered questions. For example, it is interesting to know whether the flora colonized in different ecological niches communicate and interact with each other.

2.3. Dietary factors

Besides host genotype, immune status and intestinal environment, diet also affects gut microbiota (David et al., 2014; Goodrich et al., 2014; Carmody et al., 2015; Pereira and Berry, 2017; Rothschild et al., 2018). Alterations in diet, like carbohydrates and proteins, cause rapid changes in gut microbial profiles (David et al., 2014). Although it cannot be digested by animal endogenous digestive enzymes (Raninen et al., 2011), dietary fiber regulates the abundance of the microbiotal community (Jha and Berrocoso, 2015; Liu et al., 2018; Tan et al., 2018; Wang et al., 2018a), and maintains the homeostasis of the intestinal environment (Tian et al., 2017; Luo et al., 2018; Che et al., 2019). Thus, there is a growing interest in the usage of fiber in feed to optimize the intestinal health of pigs, however, it should be noted that the effects of dietary fiber with different sources, types and levels differ.

The quantity and quality of protein also have direct effects on intestinal microbiota (Fan et al., 2015; Singh et al., 2017). Diets that contain high levels of protein result in longer intestinal transit time and higher microbiota diversity (MacFarlane et al., 1986). Low-protein diets affect pig microbiota by increasing Lachnospiraceae, Prevotellaceae, and Veillonellaceae (Chen et al., 2018; Qiu et al., 2018), while decreasing ammonia, which is one kind of microbial metabolite (Luo et al., 2015).

3. Local effects of major microbial metabolites

Since the intestinal microbiota in pigs currently includes 9,623,520 non-redundant genes (Xiao et al., 2016; Wang et al., 2019a), it is regarded as a second genome with functions that the host cannot perform in most situations (Backhed et al., 2005; Guevarra et al., 2019). Gut microbiota is pivotal for the health and well-being of animals (Stokes, 2017), which is largely dependent on microbial metabolism (Human Microbiome Project, 2012). The
well-known metabolites in the colon are SCFA from dietary fiber fermentation, including acetate, propionate and butyrate (Pascale et al., 2018; Koh et al., 2016; Oliphant and Allen-Vercoe, 2019). Interestingly, the chemical structure of the fermentable fibers determines the production of SCFA, for example inulin is propionogenic, and resistant starches are more butyrogenic (Rastelli et al., 2019). SCFA have lots of effects in gut mechanisms. Mechanistically, SCFA are rapidly transported by monocarboxylate transporters (MCT) to enter the citric acid cycle (Daille et al., 2019). Other possible mechanisms include G protein-coupled receptors (GPR)-mediated cellular signaling and histone deacetylase (HDAC)-mediated epigenetic modifications (Yang et al., 2018). SCFA are also transported into portal circulation as an energy substrate for hepatocytes (Schonfeld and Wojtczak, 2016) and into the circulatory system (Daille et al., 2019) to perform microbiota-gut-brain cross-talk (Sarkar et al., 2016).

In contrast to carbohydrate metabolism by the gut microbiota, proteolysis is less extensively researched. It should be noted that microbial fermentation of proteins produces a variety of metabolites, which are generally considered to be harmful to intestinal integrity and metabolism (Nyangale et al., 2012; Zhao et al., 2018). For example, the microbial metabolite of histidine, imidazole propionate, has been shown to be a major risk factor for insulin resistance and type 2 diabetes (Koh et al., 2018). However, microbial metabolites from tryptophan have benefits for health (Agus et al., 2018). Tryptophan is mainly metabolized through the kynurenine pathway, 5-hydroxytryptamine (5-HT) pathway and indole/aryl hydrocarbon receptor (AHR) pathway (Alkhalaf and Ryan, 2015; Agus et al., 2018). Although most of tryptophan ingested is digested and absorbed in the small intestine, tryptophan reaches the colon (Morales et al., 2016; Yao et al., 2016) to be degraded by a series of symbiotic bacteria into effective immune-modulating products (Islam et al., 2017).

Indole is a major tryptophan metabolite that is metabolized by many species of Bacteroides and Enterobacteriaceae (Roager and Licht, 2018). The function of indole includes affecting the integrity of intestinal epithelial barrier (Bansal et al., 2010), regulating intestinal immunity (Lamas et al., 2016), preventing death after chemical colitis (Shimada et al., 2013), as well as affecting lifespan of the host (Sonowal et al., 2017). Tryptamine is a neurotransmitter that activates the 5-HT4 receptor expressed in colon epithelial cells to control colonic transport (Bhattarai et al., 2018; Cryan et al., 2018). Tryptamine also enhances immune surveillance and inhibits the expression of pro-inflammatory cytokines (Tourino et al., 2013; Islam et al., 2017). Indole 3-propionate affects host intestinal inflammation (de Mello et al., 2017; Tuomainen et al., 2018), glucose metabolism, gut barrier and immune response (Zhang and Davies, 2016; Dodd et al., 2017).

4. Indirect effects of major microbial metabolites: microbiota-gut-brain axis

Currently, the MGBA has been well-established, and the microbiota is an important regulator in this axis (Cryan et al., 2019). Metabolites of intestinal flora impact brain function via the vagus nerve, blood–brain barrier (BBB) and immune system (Fig. 1) (Borre et al., 2014; Forsythe et al., 2014; Erny et al., 2015; O’Mahony et al., 2015; Daille et al., 2019; Silva et al., 2020).

4.1. Vagus nerve

The vagus nerve contains sympathetic and parasympathetic nerves, including about 80% of the afferent nerve fibers and 20% of the efferent nerve fibers (Napadow et al., 2012). This anatomical structure makes the vagus nerve a bridge between the intestine and central nervous system (CNS) (Bonaz et al., 2018). Vagal nerve fibers express receptors of 5-hydroxytryptamine and free fatty acid receptors (FFAR) (Nohr et al., 2013, 2015), resulting in ideally transmitted signals from the gut to the brain (Bonaz et al., 2018). Notably, gut microbes, such as Bifidobacterium longum NCC3001, Lactobacillus rhamnosus JB-1 and Lactobacillus reuteri, fail to affect brain functions after vagotomy (Bercik et al., 2011; Bravo et al., 2011; Pouthaisidis et al., 2013; Buffington et al., 2016; Sherwin et al., 2019), suggesting that the vagus nerve plays an important role in gut microbiota-brain cross-talk (Fulling et al., 2019). However, not all communication signals between microorganisms and the brain are mediated by the vagus nerve (Mayer et al., 2015). The anxiety behavior of mice caused by mild gastrointestinal infection is still obvious after vagotomy, indicating that the vagus nerve is not the only way of mediating the anxiety caused by gastrointestinal infection (Chu et al., 2019).

4.2. Blood brain barrier

The BBB is a kind of semi-permeable structure segregating peripheral blood from the brain (Rustenhoven and Kipnis, 2019). As MCT expressed in endothelial cells of BBB, SCFA may go through the BBB (Vijay and Morris, 2014; Perez-Escuredo et al., 2016; Daille et al., 2019). Besides crossing the BBB, SCFA appear to be strategic in maintaining the integrity of the BBB. For example, germ-free mice exhibit low expression of tight junction proteins, resulting in increased permeability of the BBB (Braniste et al., 2014). Notably, the integrity of the BBB can be restored by replanting complex flora or a single bacterium that produces pro SCFA (Braniste et al., 2014). Similarly, propionate treatment alleviates the permeability of cerebral vascular endothelial cells after exposure to lipopolysaccharide (Hoyles et al., 2018).

4.3. Immune system of central nervous system

The nervous immune system is related to a series of processes including the development, function, aging and injury of the CNS (Hickman et al., 2018). Microglia are the main immune cells (Hong et al., 2016; Chu et al., 2019; Wilton et al., 2019). The metabolism of gut microorganisms regulates the maturation as well as function of microglia (Erny et al., 2015; Colpitts and Kasper, 2017). Microglia from germ-free mice or antibiotic-treated mice exhibit an immature phenotype compared with microglia from normal mice (Reemst et al., 2016). Interestingly, in both cases, oral administration of a mixture of the 3 major SCFA are sufficient to promote the maturation of microglia (Reemst et al., 2016), suggesting that SCFA regulate the homeostasis of microglia. Similarly, germ-free mice with GPR43 deficiency also show microglial defects (Erny et al., 2015), suggesting that SCFA and GPR43 are required to maintain the homeostasis of microglia. In addition, the alterations of intestinal microbial diversity induced by antibiotics affect neuroinflammation and change the morphology of microglia (Jang et al., 2018). Interestingly, sodium butyrate reduces the activation of microglia and the secretion of pro-inflammatory cytokines after lipopolysaccharide challenge (Wang et al., 2018b; Yamawaki et al., 2018). Likewise, acetate treatment reduces inflammatory responses in primary microglia (Sokol et al., 2012). Indole is also increasingly considered to be essential in the cross-talk of microbiota and a host, especially the brain immune responses (Dodd et al., 2017; Agus et al., 2018). For example, indole crosses the BBB and decreases pro-inflammatory activities via activating AHR in astrocytes (Rothhammer et al., 2016).
5. Summary and future directions

Under the modern intensive breeding model, pigs are usually kept in barren environments, resulting in various psychological problems. These psychological problems in pigs may lead to weight loss, accumulation of subcutaneous fat and poor meat quality, resulting in severe economic losses in swine production. Given that the metabolites of tryptophan and dietary fiber regulate behavior and CNS function, such as cognitive function, it could be fruitful to alleviate the psychological problems in pigs with these metabolites. However, cautious should be exercised when we apply this knowledge to pigs because our current understanding of MGBA is mainly derived from mouse models, and there are different physiological and metabolical characteristics between mice and pigs. Thus, a thorough understanding of the mechanism in which those metabolites participate, and the complex gut-brain interaction, especially in pigs, may help to propose new strategies for improving swine health. Fortunately, our scientific community has conducted seminal studies in this field. For example, intestinal perfusion with mixed antibiotics and corn starch in fistula pigs affects the concentrations of aromatic amino acids, serotonin and dopamine in the hypothalamus and regulates the expression of neurotransmitters in the brain (Gao et al., 2018, 2019). In addition, dietary tryptophan supplementation increases reproductive performance and milk yield of sows (Miao et al., 2019), while reducing the time and times of fighting among piglets, and the stress responses of weaned piglets after mixed herd rearing (Koopmans et al., 2005). Dietary fiber also affects the welfare and behavior of piglets (de Leeuw et al., 2008; Superchi et al., 2017; Jiang et al., 2019). Overall, the research on the interaction between the host and gut microbes...
allows us to see the huge regulatory potential of microbial metabolites for host health.

Author contributions

Lijuan Fan: writing-original draft preparation, visualization; Bingnan Liu and Ziyi Han: writing-reviewing and editing; Wenkai Ren: conceptualization, methodology, writing-reviewing and editing.

Conflict of interest

We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work.

Acknowledgement

This study was supported by the National Natural Science Foundation of China (31922079, 31827365, and 31790411) and Guangdong Basic and Applied Basic Research Foundation (2019B151520002).

References

Aguir A, Plancheis J, Sokol H. Gut microbiota regulation of tryptophan metabolism in health and disease. Cell Host Microbe 2018;23:716–24. https://doi.org/10.1016/j.chom.2018.05.003.
Alain BFE, Chae JP, Balolong MP, Bum Kim H, Kang DK. Assessment of fecal bacterial diversity among healthy piglets during the weaning transition. J Gen Microbiol 2014;160:160–6. https://doi.org/10.1099/jgm.0.2013.003493.
Albenberg L, Esipova TV, Judge CP, Bittinger K, Chen J, Laughlin A, et al. Correlation between microbial membrane fatty acids and immune function and health in children. J Infect Dis 2021;223:991–1003. https://doi.org/10.1093/infdis/jiaa236.
Amit T, Alony Y, Wood TK, Jayaraman A. The bacterial signal indole increases epithelial-cell tight-junction resistance and attenuates indicators of inflammation. Proc Natl Acad Sci U S A 2010;107:228–33. https://doi.org/10.1073/pnas.0906121107.
Berck P, Park AJ, Song D, Khoshdel A, Lu J, Huang X, et al. The anxiolytic effect of Bifidobacterium longum NCC3001 involves vagal pathways for gut-brain communication. Neurogastroenterol Motil 2015;27:1542–9. https://doi.org/10.1111/nmm.12746.
Bhatnagar Y, Williams BB, Battaglioli EJ, Whitaker WR, Till L, Grover M, et al. Gut microbiota-produced tryptamine activates an epithelial G-protein-coupled receptor to increase colonic secretion. Cell Host Microbe 2018;23:775–86. https://doi.org/10.1016/j.chom.2018.05.003.
Bchir AF, Chirouze M, Vaurio H, Venet P, Dahan A, Nakamura K, et al. Microbial reconstitution reverses maternal diet-induced social and synaptic plasticity in offspring. Cell 2016;165:1762–78. https://doi.org/10.1016/j.cell.2016.06.001.
Bostian KA, Britton W, Varady KA, Gao R, Martin J, Bulich G, et al. Gut microbiota influence of the gut microbiota on maternal metabolism. Mol Metab 2018;30:123–33. https://doi.org/10.1016/j.molmet.2018.08.016.
Boyaci P, Wang R, Xu J, Lu L, Xu Z, Zhu W, et al. Microbiota alters tryptophan metabolism through the vagus nerve to control glucose control. Cell Metab 2015;22:317–28. https://doi.org/10.1016/j.cmet.2015.02.005.
Buchfuhrer J, Rey FE, Sonnenburg JL, Peterson DA, Gordon JL. Host-bacterial mutualism in the human intestine. Science 2005;307:1915–20. https://doi.org/10.1126/science.1104816.
Bai T, Alain R, Wood TK, Jayaraman A. The bacterial signal indole increases epithelial-cell tight-junction resistance and attenuates indicators of inflammation. Proc Natl Acad Sci U S A 2010;107:228–33. https://doi.org/10.1073/pnas.0906121107.
Berrin J, Creed P, Spitzer MH, Van Treuren W, Merrill BD, Hryckowian AJ, Higginbottom SK, et al. Diet rapidly and reproducibly alters the gut human microbiome. Nature 2014;505:559–63. https://doi.org/10.1038/nature12820.
Bush de Leeuw JA, Bolhuis JE, Bosch G, Gerrits WJ. Effects of dietary fibre on behaviour and satiety in pigs. Proc Nutr Soc 2008;67:334–42. https://doi.org/10.1017/S0033283X080083X.
De Mello VP, Paananen J, Lindstrom J, Lankinen MA, Shi L, Kuusiisto J, et al. Indole-3-lactic acid and novel lipid metabolites are associated with a lower risk of type 2 diabetes in the Finnish Diabetes Prevention Study. Sci Rep 2017;7:46337. https://doi.org/10.1038/s41598-017-07157-9.
Dodd D, Spitzer MH, Van Treuren W, Merrill BD, Hryckowian AJ, Higginbottom SK, et al. A gut bacterial pathway metabolizes aromatic amino acids into nine circulating metabolites. Nature 2017;551:64–52. https://doi.org/10.1038/nature24651.
Donaldson GP, Lee SM, Mazmanian SK. Gut biogeography of the bacterial microbiota. Nat Rev Microbiol 2016;14:20–32. https://doi.org/10.1038/nrmicro3552.
Enev H, Drabe de Angelis AL, Jaitin D, Wieghofer P, Szaszewska D, David E, et al. Host microbiota constantly control maturation and function of the CNS. Nat Microbiol 2015;18:965–73. https://doi.org/10.1038/nm.4030.
Espey MG. Role of oxygen gradients in shaping redox relationships between the human intestine and its microbiota. Free Radic Biol Med 2015;73:1146–50. https://doi.org/10.1016/j.freeradbiomed.2015.06.007.
Fan P, Li L, Rezaei A, Eslamifard S, Che D, Ma X, Metabolites of dietary protein and peptides by intestinal microbes and their impacts on gut. Curr Protein Pept Sci 2015;16:646–54. https://doi.org/10.2174/13892036156666100313657.
Forsythe P, Bienstock J, Kunze WA. Vagal pathways for microbiome-brain-gut communication. Adv Exp Med Biol 2018;7:115–33. https://doi.org/10.1007/978-1-4939-0897-4_5.
Frese SA, Parker K, Calvert CC, Mills DA. Diet shapes the gut microbiome of pigs during nursing and weaning. Microbiome 2015;3:28. https://doi.org/10.1186/s40168-014-0091-8.
Fulling C, Dinan TG, Cryan JF. Gut microbiota to brain signaling: what happens in vagus. Neuron 2019;101:998–1002. https://doi.org/10.1016/j.neuron.2019.02.008.
Gao K, Li Y, Mu CL, Farzi A, Liu Z, Zhu WY. Increasing carbohydrate availability in the hindgut promotes hypothalamic neurotransmitter synthesis: aromatic amino acids linking the microbiota-brain axis. J Neurochem 2019;149:641–59. https://doi.org/10.1111/jnc.14709.
Gao K, Li Y, Mu CL, Peng Y, Huang Z, Zhu WY. Antibiotics-induced modulation of large intestinal microbiota altered aromatic amino acid profile and expression of neurotransmitters in the hypothalamus of piglets. J Neurochem 2018;146:219–34. https://doi.org/10.1111/jnc.14333.
Gheorghe CE, Martin JA, Manriquez FV, Dinan TG, Cryan JF, Clarke G. Focus on the essentials: tryptophan metabolism and the microbiome-gut-brain axis. Curr Opin Pharmacol 2019;48:137–45. https://doi.org/10.1016/j.coph.2019.08.004.
Goodrich JK, Waters JL, Poole AC, Sutter JL, Koren O, Blekman R, et al. Human gut microbiota shape the gut microbiome. Cell 2014;159:789–99. https://doi.org/10.1016/j.cell.2014.09.053.
Guevarra RB, Hong SH, Cho JH, Kim BR, Shin J, Lee JE, et al. The dynamics of the piglet gut microbiome during the weaning transition in association with health and nutrition. J Anim Sci Biotechnol 2018;9:54. https://doi.org/10.1186/s40104-018-0269-9.
Guevarra RB, Lee JH, Lee SH, Seok MJ, Kim DW, Kang BN, et al. Piglet gut microbiota shifts early in life: causes and effects. J Anim Sci Biotechnol 2019;10:1. https://doi.org/10.1186/s40104-019-0336-4.
Heinritz MS, Mosenthin R, Weiss E. Use of pigs as a potential model for research into dietary modulation of the gut microbiota. Nutr Res Rev 2013;26:191–209. https://doi.org/10.1111/j.1753-4887.2013.00152.x.
Hickman S, Izzy S, Sen P, Morselt L, El Khoury J. Microglia in neurodegeneration. Nat Neurosci 2018;21:1359–71. https://doi.org/10.1038/s41593-018-0124-x.
Hong S, Beja-Classer VF, Nfonnyim BM, Frouin A, Li S, Ramakrishnan S, et al. Complement and microbiota mediate early synapse loss in Alzheimer mouse models. Science 2016;352:712–6. https://doi.org/10.1126/sciadv.aad3873.

Hoyles L, Snelling T, Umlauft UK, Nicholson JK, Carding SR, Glen RC, et al. Microbiome-host interactions: protective effects of propionate upon the blood-brain barrier. Microbiome 2018;6:55. https://doi.org/10.1186/s40168-018-0439-y.

Huang S, Li N, Liu C, Li T, Wang W, Jiang L, et al. Characteristics of the gut microbiota colonization, inflammatory profile, and plasma metabolome in intravenous growth restriction during the last 10% of gestation. J Microbiol 2019;57:748–58. https://doi.org/10.1007/s12275-019-8690-x.

Human Microbiome Project C. Structure, function and diversity of the healthy human microbiome. Nature 2012;486:207–14. https://doi.org/10.1038/ncomms13124.

Islam J, Sato S, Watanabe K, Watanabe T, Ardasianys, Hirahara K, et al. Dietary tryptophan alleviates dextran sodium sulfate-induced colitis through aryl hydrocarbon receptor in mice. J Nutr Biochem 2017;42:43–50. https://doi.org/10.1016/j.jnutbio.2017.07.006.

Jang HM, Lee HJ, Jang SE, Han MJ, Kim DH. Evidence for interplay among antibacterial-induced gut microbiota disturbance, neuro-inflammation, and anxiety in mice. Mucosal Immunol 2018;11:1386–97. https://doi.org/10.1038/s41385-018-0452-3.

Jha R, Berrocoso J. Review: dietary fiber utilization and its effects on physiological functions and gut health of swine. Animal 2015;9:1441–52. https://doi.org/10.1017/S1751731114000808.

Jiang X, Lu N, Xue Y, Liu S, Lei H, Tu W, et al. Crude fiber modulates the fecal microbiome and steroid hormones in pregnant Meishan sows. Gen Comp Endocrinol 2019;277:141–7. https://doi.org/10.1016/j.ygeno.2019.04.006.

Kelly J, Daly K, Moran AW, Ryan S, Bravo D, Shirazi-Beechey SF. Composition and diversity of microbial communities of the pig gastrointestinal tract; diets, environment. Environ Microbiol 2017;19:1425–38. https://doi.org/10.1111/1462-2920.13619.

Kim HB, Chao Y, Song RS, Seo YJ, Jeong SD, Song JH, et al. Dietary fiber modulates short chain fatty acids and RAS/MAPK activity in the distal gut of growing pigs. Cell 2018;175:947. https://doi.org/10.1016/j.cell.2018.09.055.

Kim, Isaacson RE. The pig gut microbial diversity: understanding the pig gut microbiome. Vet Microbiol 2015;177:242 https://doi.org/10.1016/j.vetmic.2015.01.041.

Kim HB, Borewicz K, White BA, Singer RS, Sreevatsan S, Tu ZJ, et al. Microbial shifts during lactation affect milk yield and composition in lactating sows. J Dairy Sci 2015;98:125–32. https://doi.org/10.3168/jds.2014-8682.

Kim KB, van Kranenburg R, Zhou Y, Liu H, Kong Y, et al. Gut microbiota and cardiovascular function: importance of fiber type and quality. Am J Physiol Gastrointest Liver Physiol 2018;314:L515–31. https://doi.org/10.1152/ajpgi.00344.2018.

Kim, R. Berrocoso J. Review: dietary fiber utilization and its effects on physiological functions and gut health of swine. Animal 2015;9:1441–52. https://doi.org/10.1017/S1751731114000808.

Kim, Isaacson RE. The pig gut microbial diversity: understanding the pig gut microbiome. Vet Microbiol 2015;177:242 https://doi.org/10.1016/j.vetmic.2015.01.041.

Kim KB, van Kranenburg R, Zhou Y, Liu H, Kong Y, et al. Gut microbiota and cardiovascular function: importance of fiber type and quality. Am J Physiol Gastrointest Liver Physiol 2018;314:L515–31. https://doi.org/10.1152/ajpgi.00344.2018.

Koh A, Borewicz K, White BA, Singer RS, Sreevatsan S, Tu ZJ, et al. Microbial shifts during lactation affect milk yield and composition in lactating sows. J Dairy Sci 2015;98:125–32. https://doi.org/10.3168/jds.2014-8682.
Singh RK, Chang HW, Yan D, Lee KM, Ucmak D, Wong K, et al. Influence of diet on the gut microbiome and implications for human health. J Transl Med 2017;15:73. https://doi.org/10.1186/s12967-017-1175-y.

Soliman ML, Puig KG, Combs CK, Rosenberger TA. Acetate reduces microglia inflammatory signaling in vitro. J Neurochem 2012;123:555–67. https://doi.org/10.1111/j.1471-4159.2012.07953.x.

Sonowal R, Swimm A, Sahoo A, Luo L, Matsunaga Y, Wu Z, et al. Indoles from commensal bacteria extend healthspan. Proc Natl Acad Sci U S A 2017;114: E7506–15. https://doi.org/10.1073/pnas.1706464114.

Stearns JC, Lynch MD, Senadheera DB, Tenenbaum HC, Goldberg MB, Cvitkovich DG, et al. Bacterial biogeography of the human digestive tract. Sci Rep 2011;1:170. https://doi.org/10.1038/srep00170.

Stilling RM, van de Wouw M, Clarke G, Stanton C, Dinan TG, Cryan JF. The neuropharmacology of butyrate: the bread and butter of the microbiota-gut-brain axis? Neurochem Int 2016;99:110–32. https://doi.org/10.1016/j.neuci.2016.06.011.

Stokes CR. The development and role of microbial-host interactions in gut mucosal immune development. J Anim Sci Biotechnol 2017;8:12. https://doi.org/10.1186/s40104-016-0138-0.

Superchi P, Saleri R, Borghetti P, Ferrarini G, Cavalli V, Sereni M, et al. Effects of a dietary crude fibre concentrate on growth in weaned piglets. Animal 2017;11:1905–12. https://doi.org/10.1017/S175173111700057X.

Tan CQ, Sun HQ, Wei HK, Tan J, Long G, Jiang SW, et al. Effects of soluble fiber inclusion in gestation diets with varying fermentation characteristics on lactational feed intake of sows over two successive parities. Animal 2018;12:1388–95. https://doi.org/10.1017/S1751731170030195.

Tian L, Bruggeman G, van den Berg M, Borewicz AJ, Bruininx E, et al. Effects of pectin on fermentation characteristics, carbohydrate utilization, and microbial community composition in the gastrointestinal tract of weaning pigs. Mol Nutr Food Res 2017;61. https://doi.org/10.1002/mnfr.201600186.

Tourino MC, de Oliveira EM, Belle LP, Kleinh FB, Albuquerque RC, Dorr FA, et al. Tryptamine and dimethyltryptamine inhibit indoleamine 2,3 dioxygenase and increase the tumor-reactive effect of peripheral blood mononuclear cells. Cell Biochem Funct 2013;31:361–4. https://doi.org/10.1002/cbf.2980.

Tropini C, Earle KA, Huang KC, Sonnenburg JL. The gut microbiome: connecting spatial organization to function. Cell Host Mboke 2017;21:433–42. https://doi.org/10.1016/j.chom.2017.09.010.

Tuomainen M, Lindstrom J, Lehtonen M, Aurioja S, Pihlajamaki J, Peltonen M, et al. Associations of serum indolepropionic acid, a gut microbiota metabolite, with type 2 diabetes and low-grade inflammation in high-risk individuals. Nutr Diabetes 2018;8:35. https://doi.org/10.1038/s41387-018-0046-9.

Vijay N, Morris ME. Role of monocarboxylate transporters in drug delivery to the brain. Curr Pharmaceut Des 2014;20:1487–98. https://doi.org/10.2174/13816128113199900462.

Von Mutius E. The shape of the microbiome in early life. Nat Med 2017;23:274–5. https://doi.org/10.1038/nm.4299.

Wang C, Li P, Yan Q, Chen L, Li T, Zhang W, et al. Characterization of the pig gut microbiome and antibiotic resistome in industrialized feedlots in China. mSystems 2019a;4. https://doi.org/10.1128/mSystems.00206-19.

Wang J, Qin C, He T, Qu K, Sun W, Zhang X, et al. Alfalfa-containing diets alter luminal microbiota structure and short chain fatty acid sensing in the caecal mucosa of pigs. J Anim Sci Biotechnol 2018a;9:11. https://doi.org/10.1186/s41040-017-0216-y.

Wang P, Zhang Y, Gong Y, Yang R, Chen Z, Hu W, et al. Sodium butyrate triggers a functional elongation of microglial process via Akt-small RhoGTPase activation and HDACs inhibition. Neurobiol Dis 2018b;111:12–25. https://doi.org/10.1016/j.nbd.2017.12.006.

Wang X, Tsai T, Deng F, Wei X, Chai J, Krapp J, et al. Longitudinal investigation of the swine gut microbiome from birth to market reveals stage and growth performance associated bacteria. Microbiome 2019b;7:109. https://doi.org/10.1186/s40168-019-0721-7.

Wilton DK, Dissing-Olesen L, Stevens B. Neuron-glia signaling in synapse elimination. Annu Rev Neurosci 2018;41:107–27. https://doi.org/10.1146/annurev-neuro-070918-050306.

Xiao L, Estelle J, Kiiplerich P, Ramayo-Calda y, Xia Z, Feng Q, et al. A reference gene catalogue of the pig gut microbiome. Nat Microbiol 2016;1:161. https://doi.org/10.1038/nmicrobiol.2016.161.

Yamawaki Y, Yoshioka N, Nozaki K, Ino H, Oda K, Harada K, et al. Sodium butyrate abolishes lipopolysaccharide-induced depression-like behaviors and hippocampal microglial activation in mice. Brain Res 2018;1680:13–38. https://doi.org/10.1016/j.brainsci.2017.12.004.

Yang Guan, Chen Siyuan, Deng Baichuan, Tan Chengquan, Deng Jinping, Zhu Guoqiang, et al. Implication of G Protein-Coupled Receptor 43 in Intestinal Inflammation: A Mini-Review. Front Immunol. 2018;Jun 22. https://doi.org/10.3389/fimmu.2018.01434.

Yao CK, Muir JG, Gibson PR. Review article: insights into colonic protein fermentation, its modulation and potential health implications. Aliment Pharmacol Ther 2016;43:181–96. https://doi.org/10.1111/apt.13456.

Zhang L, Wu W, Lee YK, Xie J, Zhang H. Spatial heterogeneity and Co-occurrence of mucosal and luminal microbiome across swine intestinal tract. Front Microbiol 2018;9:48. https://doi.org/10.3389/fmicb.2018.00048.

Zhang LS, Davies SS. Microbial metabolism of dietary components to bioactive metabolites: opportunities for new therapeutic interventions. Genome Med 2016;8:46. https://doi.org/10.1186/s13073-016-0296-x.

Zhao L, Zhang F, Ding X, Wu G, Lam YY, Wang X, et al. Gut bacteria selectively influence of diet on the gut microbiome and implications for human health. J Transl Med 2017;15:17–23. https://doi.org/10.1186/s12967-017-1175-y.

Zhu Guoqiang, et al. Implication of G Protein-Coupled Receptor 43 in Intestinal Inflammation: A Mini-Review. Front Immunol. 2018;Jun 22. https://doi.org/10.3389/fimmu.2018.01434.