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Prokaryotes Rule the World

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Abstract

For millions of years, prokaryotic organisms have functioned as a vital selective force shaping eukaryotic evolution. It is now widely accepted that gut bacteria play a vital role in various physiological and metabolic activities of hosts, and thus, it is essential to maintain their homeostasis. Previous studies have shown an association of gut bacterial imbalance (dysbiosis) associated with several pathologies. However, very little is known about possible mechanisms involved between bacteria and hosts to maintain their homeostasis in the gut. Bacterial activities, such as cooperation (biofilm formation, horizontal gene transfer, quorum sensing, etc.), antagonism, and combination, and host responses of their immune system, gut barrier functions, and different dietary components have been identified as crucial factors for maintaining bacterial homeostasis in the gut. Our understanding of several possible mechanisms involved in gut bacterial homeostasis should be widened to modulate their composition or treat diseases. The objective of this chapter is to provide an overview of different factors involved in gut bacterial homeostasis with an emphasis on host intestinal barrier and immune system, dietary components, and quorum sensing. Also, brief information regarding roles of microbiota on gut-brain axis has also been included.

Keywords: prokaryotes, *quorum sensing*, gut microbial homeostasis, microbiome

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1. Background

It is now well-established fact that almost any metazoan either invertebrates or vertebrates harbor gut microbiota [1]. Complex and diverse bacterial populations were reported from the alimentary tract of humans which were previously estimated to be around 10^{14} [2]. Moreover, the total microbiome present in a human was estimated to be 10 times higher than the total

number of their somatic and germ cells [2]. On the contrary, a recent study showed the variations in gut bacterial number from 10^7 (Stomach, Duodenum, and Jejunum) to 10^{14} (Colon) and estimated the almost equal number of total bacterial and human cells [3]. Approximately, 3.3 million nonredundant genes were reported to be present in the microbiome of the human gut, whereas only around 20,000 genes were present in a human genome suggesting substantial genetic diversities of microbial populations [4]. Besides, more than 99% of these genes represent 1000–1150 different bacterial species [5] which suggests the presence of diverse and complex microbiota in the gut of humans.

During these days, there has been enormous progress in sequencing technologies regarding both increasing the throughput and decreasing the cost and error rate. Significant efforts have been made in characterizing compositions and functions of microbiota along with this advancement in sequencing technologies and have reported complex and diverse groups of microbiota residing in various regions of hosts including skin, oral cavity, nasal cavity, urogenital tract, and gut [5, 6]. Such type of variations can occur not only among different regions but can also within different locations of the same area (e.g., lumen vs. mucosa of the gut), as shown in **Figure 1** [7]. Among various microbes residing inside and outside of both humans and animals, bacteria living in the gut have been widely studied and have been found to have an effect on health and diseases through complex interactions with their hosts. Various factors such as diets, antibiotics, a method of delivery and infant feeding, illness, stress, aging, lifestyles, and host genetics can affect gut microbiota [8, 9]. The proper balance

Figure 1. PCoA plot showing significant difference in bacterial community structure among different regions and locations of gastrointestinal tract of 3-week old chickens. MRS-recovered cells from cecal lumen (M-CL), cecal mucosa (M-CM) and ileal mucosa (M-IM), and total bacterial cells from cecal lumen (T-CL) (ANOSIM results; $R = 0.67$, $p = 0.001$). This figure is adapted from reference [7], figure 6(A).

of microbiota is needed to maintain microbial homeostasis inside gut, which potentially affect the health of individuals. Change in composition of gut microbiota by any factors as described earlier is called dysbiosis, which can cause several diseases and disorders including allergies, inflammatory bowel disease (IBD), diabetes, cancer, and autism as reviewed earlier [8]. Even though detail mechanisms that are responsible for maintaining gut microbial homeostasis need to be explored more in the future, host intestinal barrier and immune system, dietary components and Quorum sensing are some of the critical mechanisms identified and studied so far [10].

2. Intestinal barrier and host immune system for maintaining microbial homeostasis

Prokaryotes are prevalent in all environments [11, 12] having to live in mutualism with eukaryotes [13–16]. Adaptive diversification is a process intrinsically tied to species interactions [17]. The endosymbiotic theory states that several vital organelles of eukaryotes originated as symbioses between separate single-celled organisms [18, 19]. Hence, organelles such as mitochondria and plastids once free-living bacteria that were taken by the more important cell as an endosymbiont [20–22]. The microbiome of the gastrointestinal tract (GIT) contains over 50 genera and at least 1000 different species [23–29], and the cecum and colon of humans, harbor $\sim 10^{13}$ cfu/g [29], covering to 40–55% of solid stool matter and weights [30–32]. The microbiome modulates the development of the innate and acquired immune system [33–35], gastrointestinal physiology [36–41] and digestibility of nutrients [42–46] of metazoans. Many factors including nutrient composition, stress, and antibiotics can alter the microbiome [47–51]. In fact, the western obesogenic diet is associated to induce and promote several metabolic disorders and cancer [52–58]. Microbiome and its host are working as one single organism. One of the fascinating aspects of this mutualism is the impact in the regulation of inflammatory responses [59–63]. Enterocytes not only participate in digestion and absorption of nutrients, but they also involve as antigen presenting cells and regulates gut permeability. The host's intestinal epithelial cells provide both physical and chemical barriers to pathogenic bacteria through the production of mucus, secretion of antimicrobial peptides from Paneth cells, IgA from plasma cells, forming intercellular tight junction complexes, and recognition of MAMP [63, 64]. Furthermore, specific products that are synthesized and secreted from symbionts can prevent colonization of pathogenic or opportunistic commensal bacteria. For instance, a single microbial molecule (PSA) synthesized by *Bacteroides fragilis* was found to protect from colitis induced by *Helicobacter hepaticus* through the suppression of pro-inflammatory interleukin-17 and enhancement of interleukin-10-producing CD4⁺ T cells [65]. Likewise, commensal bacteria can activate innate and adaptive immune system to eliminate pathogens through the invasion of host's epithelial cells [64]. Furthermore, commensal bacteria can play a vital role in the promotion of lipopolysaccharides (LPS) detoxification through

the activation of epithelial intestinal alkaline phosphatase (IAP) expression and can also involve in gut-associated lymphoid tissue (GALT) development and secondary bile acids formation [63].

3. Effects of different dietary components on microbial homeostasis

Various nutrients present in diets are sources of microbial metabolism and affect significantly on structure, composition, and diversities of microbiota which have been reviewed previously [66, 67]. Dietary fibers are the most common source of fuel for fermentation by human microbes among different nutritional components [68]. Dietary fibers are complex carbohydrates of plant origin which cannot be digested by the host's enzymes and need specific enzymes of microbial origin for digestion [69]. Western diets are lower in dietary fibers in comparison with traditional diets, and these differences can have a significant impact on microbiota composition and diversity. Studies have reported changes in microbiota composition, reduced microbial diversity and lower production of short chain fatty acids (SCFA) in individuals having a Western diet in comparison with those having a traditional diet [70–72]. Those carbohydrates that can be metabolically utilized by gut microbes and can affect their composition, functions and metabolic activities have recently been termed as “microbiota-accessible carbohydrates” (MACs) [68]. A recent study reported the progressive loss of microbial diversity in mice fed with low dietary MACs, which could not be recovered with higher MACs after second, third, and fourth generation [73]. Similarly, supplementation of diet with a brown seaweed *Laminaria japonica* that are higher in MACs resulted desirable shift in intestinal microbiota composition of rats through decrease in obesity-associated bacterial genera (*Allobaculum*, *Turicibacter*, *Coprobacillus*, *Mollicute*, and *Oscilibacter*), and bacterial genera with pathogenic potentials (*Mollicute*, *Bacteroides*, *Clostridium*, *Escherichia*, and *Prevotella*) and increase in Lactic acid bacteria (*Subdoligranulum*, *Streptococcus*, *Lactobacillus*, *Enterococcus*, and *Bifidobacterium*) [74]. Besides, a diet deprived in MACs can cause a detrimental impact on gut homeostasis and stimulate the development of different inflammatory diseases including allergies, infections, and autoimmune diseases as reviewed earlier [75].

Short-chain fatty acids (SCFA) such as acetate, propionate, and butyrate that are produced through fermentation of MACs by enteric microbiota play an essential role in maintaining homeostasis of gut microbiota through various activities including induction of IgA, secretion of mucus, and promotion of intestinal barrier, besides immune tolerance to commensal bacteria through indirectly regulation of B and T cells [59].

4. Interactions between prokaryotes and eukaryotes

Complex interactions occur within microbes and with their hosts through various communicating mechanisms to keep their niches homeostasis. Those interactions can be either

mutualistic or antagonistic through horizontal gene transfer, biofilm formation, and *quorum sensing* or compete for nutrients and combat with other species including pathogens through the stimulation of bacteriocins, microcins, and colicins secretion [63].

5. Communication between prokaryotes and eukaryotes

Communication/signaling between Prokaryotes such as bacteria and their eukaryotic hosts is known as interkingdom communication. For the first time, the interaction between bacteria was described in two marine bioluminescent bacteria, *Vibrio fischeri* and *Vibrio harveyi* as an autoinduction [76, 77] which was later termed as *quorum sensing* (QS) [78]. *Quorum sensing* is a cell-to-cell communication process in bacteria which enables them to monitor changes in bacterial density and alter genes expression accordingly. QS is a complicated process which involves production, detection, and response to extracellular signaling molecules known as autoinducers (AIs). An increase in population density results increases in the concentration of AIs which helps bacteria to monitor changes in their cell numbers and response collectively by changing genes expression globally. Traditionally, QS was believed to occur only among bacteria. However, several recent studies reported the existence of interkingdom communication [79, 80].

6. Communication between Gram-positive and Gram-negative bacteria

It is now accepted the fact that both Gram-positive and Gram-negative bacteria use QS. But there exist differences regarding both AIs they detect and the mechanisms they respond to respective AIs. Secreted peptides serve as the signaling molecule in Gram-positive bacteria. Peptides are synthesized inside bacterial cells and are modified through processing and cyclization during the process of secretion fascinated with specialized transporters [81–85]. Once secreted peptides reach a threshold concentration, they are detected at the bacterial surface by the sensor protein which enables bacterial cells to modulate gene expression at a population level [86]. Some peptides produced by these bacteria bind membrane-bound histidine kinase receptor inducing phosphorylation responses with the consequent activation of gene expression in the QS regulon. [87]. In sum, QS in Gram-positive bacteria occur by using secreted peptides through a two-component system that consists of membrane-bound histidine kinase receptor and a cognate cytoplasmic response regulator that regulates transcription.

Gram-negative bacteria typically use acyl-homoserine lactones (AHLs) as an autoinducer in QS [88]. These bacteria can utilize other signaling molecules like AI-2 and CAI-1 whose production is mainly dependent on S-adenosylmethionine (SAM) as a substrate [89]. LuxI/LuxR regulatory system of *V. fischeri* is a typical example of QS in Gram-negative bacteria [90]. LuxI catalyzes synthesis of AHLs and LuxR which is a cytoplasmic receptor regulates

transcriptional factor after binding with AHLs. Thus, in Gram-negative bacteria QS regulatory system, AIs receptor is a cytoplasmic receptor whereas membrane-bound in case of Gram-positive bacteria. Similarly, the AIs in case of Gram-negative bacteria can diffuse in and out of the cell. In contrast, in Gram-positive bacteria, those molecules need to be transported.

7. Communication between bacteria and hosts

Communication between bacteria and hosts involves hormones produced by host and hormones, that is, autoinducers (AIs) produced by bacteria [91]. The hormones produced by hosts can be divided into three broad categories: protein or peptides, steroid, and amines. Among them, protein or peptides serve as prohormones. Other hormones such as epidermal growth factor (EGF), insulin, glucagon, and amine hormones such as catecholamines, adrenaline, noradrenaline (NA), dopamine are some of the essential hosts' hormones involved in interkingdom signaling [92].

The presence of specific bacterial receptors of these hormones produced by mammalian cells is a crucial factor for communication between them. QS is affected by different mammalian hormones and the ways of sensing by bacteria to modulate their activities. As described earlier [92], adrenaline and noradrenaline (A and NA) secreted by mammalian cells are detected by bacterial membrane-bound histidine kinases (QseC and QseE). Also, QseC and QseE sense bacterial AI-3 signaling and sources of sulfates (SO_4) and phosphates (PO_4), respectively. These signalings phosphorylate KdpE, QseB, and QseF that leads to activate the expression of T3SS, motility, and Shiga toxin. Dynorphin, which is a crucial neuropeptide involved in the stress signal [93], has been found to enter into bacterial cells and sensed by MvfR/PqsR receptor leading to increase in virulence of bacteria through *quorum sensing*, through direct or indirect sensing of dynorphin by MvfR/PqsR needs to be explored. Lipid hormones such as estrone, estradiol, and estriol can enter into bacterial cells and effect on LuxR-type regulators that inhibit *quorum sensing*, albeit it is not clear whether LuxR-type regulators are the receptors of those hormones or not. Although receptors for natriuretic peptides are not known, they are found to promote virulence, biofilm formation, and lipopolysaccharides (LPS) modifications in bacteria.

Apart from those host's hormones and bacterial receptors as described above, there are several examples where bacteria sense host's hormones. Gastrin has been associated with an increase in the growth of *H. pylori*. Also, *H. pylori* infection has been found to associate with an increase in gastrin secretion suggesting the interkingdom communication [92]. Other examples include sensing of EGFs, opioid hormones.

Besides hormones, different nutrients such as ethanol-amine (EA) and sugars have also been reported to involve in QS. Also, bacteria can sense various components of the immune system such as cytokines, apolipoprotein B (ApoB), Nox2, and antimicrobial peptides, modulating the host immune responses [92]. The possibility of interkingdom communication between Nef protein of HIV-1 virus and the host through exosomes has been recently reviewed, which extends the existence of QS other than in bacteria [94]. Likewise, QS can occur in animals

and plants [92]. Furthermore, recent studies have demonstrated the possibilities of host microRNA-microbiota communication and emphasized needs of exploring more in the future regarding the involvement of microRNAs in QS [95, 96].

8. The microbiome-gut-brain axis

Prokaryotes in the GIT secrete or induce the secretion of several neuropeptides that participate in the communication between the enteric and the central nervous systems, involved in several aspects from brain development to inflammation and behavior [16, 97–100]. These interactions are today described by a relatively new field of study known as microbial endocrinology [101–109]. This is a two-way communication because just as prokaryotes can regulate brain activities, the central nervous system can also induce dramatic changes in the gut microbiome [110–112]. For instances, chronic ingestion of live *Lactobacillus plantarum* PS128 in germ free mice increased levels of serotonin and dopamine in the striatum suggesting the possibility of improving behaviors related to anxiety through daily intake of that particular strain of *L. plantarum* [113]. Besides, stress hormones such as adrenaline and corticosteroids can increase the virulence of enteropathogens [114–117]. Although different routes and mechanisms involved in the bidirectional communication between microbiota and brain are still being explored, some of those that have been previously described include the vagus nerve, signaling of gut hormones, bacteria derived metabolites such as SCFA, the immune system, and tryptophan metabolism [118, 119].

9. Concluding remarks

Colonization of microbiota before or after the birth of individuals is still a subject of debate [120], but it is widely accepted that methods of delivery affect the microbiota of infants. During the early life of individuals, they harbor less complex gut microbiota which changes along with their growth and becomes a conventional core microbiota at adult stage [121]. However, their composition, structure, and diversity are significantly affected by different factors such as diet, stress, medication, host-genetics, lifestyle, and so on. Dysbiosis of gut microbiota by any means can lead to severe outcomes, and thus, it is essential to maintain microbial homeostasis in the gut. A balance between pro- and inflammatory cytokines is needed to maintain gut microbial homeostasis [122]. Albeit detail mechanisms that are responsible for maintaining homeostasis between trillions of bacteria and human cells are still being explored, various microbial activities such as co-operation (biofilm formation, horizontal gene transfer, *quorum sensing* etc.), antagonism, and combination, host responses of their immune system, gut barrier functions, and different dietary components are some of the vital factors for maintaining homeostasis in the gut. Microbes (bacteria/virus) can communicate with each other and also with hosts (mammalian or no mammalian) through the use of different hormones and signal molecules as described earlier. Such communications help microbes to alter their various activities including virulence and modulate host immune responses and thus, significantly

have an effect on health and diseases of hosts. Although multiple mechanisms involved in communication between microbes and host epithelial cells as well as their roles in health and diseases are still being explored, their various activities that have been identified and studied so far are so fascinating and seem that they are ruling the eukaryotes.

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References

- [1] Lee W, Hase K. Gut microbiota-generated metabolites in animal health and disease. *Nature Chemical Biology*. 2014;**10**(6):416-424. DOI: 10.1038/nchembio.1535
- [2] Luckey TD. Introduction to intestinal microecology. *The American Journal of Clinical Nutrition*. 1972;**25**(12):1292-1294
- [3] Sender R, Fuchs S, Milo R. Revised estimates for the number of human and bacteria cells in the body. *PLoS Biology*. 2016;**14**(8):e1002533
- [4] Turnbaugh PJ, Ley RE, Hamady M, et al. The human microbiome project. *Nature*. 2007;**449**:804-810. DOI: 10.1038/nature06244
- [5] Qin J, Li R, Raes J, et al. A human gut microbial gene catalogue established by metagenomic sequencing. *Nature*. 2010;**464**:59-65. DOI: 10.1038/nature08821
- [6] Huttenhower C, Gevers D, Knight R, et al. Structure, function and diversity of the healthy human microbiome. *Nature*. 2012;**486**:207-214. DOI: 10.1038/nature11234
- [7] Adhikari B, Kwon YM. Characterization of the Culturable subpopulations of lactobacillus in the chicken intestinal tract as a resource for probiotic development. *Frontiers in Microbiology*. 2017;**8**:1389. DOI: 10.3389/fmicb.2017.01389
- [8] Zhang Y, Li S, Gan R, et al. Impacts of gut bacteria on human health and diseases. *International Journal of Molecular Sciences*. 2015;**16**(4):7493-7519. DOI: 10.3390/ijms-16047493
- [9] Wen L, Duffy A. Factors influencing the gut microbiota, inflammation, and type 2 diabetes. *The Journal of Nutrition*. 2017;**147**(7):1468S-1475S. DOI: 10.3945/jn.116.240754
- [10] Adhikari B, Kwon YM, Hargis BM, et al. How trillions of microbes residing on gastrointestinal tract maintain homeostasis with host cells? *Food and Nutritional Journal*. 2018:FDNJ-170. DOI: 10.29011/2575-7091.100070

- [11] Bronstein JL, Alarcón R, Geber M. The evolution of plant-insect mutualisms. *The New Phytologist*. 2006;**172**(3):412-428. DOI: 10.1111/j.1469-8137.2006.01864.x
- [12] Gnad F, Forner F, Zielinska DF, et al. Evolutionary constraints of phosphorylation in eukaryotes, prokaryotes, and mitochondria. *Molecular & Cellular Proteomics*. 2009;**9**(12): 2642-2653. DOI: 10.1074/mcp.M110.001594
- [13] Kikuchi Y, Hosokawa T, Nikoh N, et al. Hostsymbiont co-speciation and reductive genome evolution in gut symbiotic bacteria of acanthosomatid stinkbugs. *BMC Biology*. 2009;**7**:2. DOI: 10.1186/1741-7007-7-2
- [14] Jones EO, White A, Boots M. The evolution of host protection by vertically transmitted parasites. *Proceedings of The Royal Society B*. 2011;**278**:863-870. DOI: 10.1098/rspb.2010.1397
- [15] Saridaki A, Bourtzis K. Wolbachia: More than just a bug in insects genitals. *Current Opinion in Microbiology*. 2010;**13**(1):67-72. DOI: 10.1016/j.mib.2009.11.005
- [16] Tellez G. Prokaryotes versus eukaryotes: Who is hosting whom? *Frontiers in Veterinary Science*. 2014;**14**:1-3. DOI: 10.3389/fvets.2014.00003
- [17] Xie J, Vilchez I, Mateos M. Spiroplasma bacteria enhance survival of *Drosophila hydei* attacked by the parasitic wasp *Leptopilina heterotoma*. *PLoS One*. 2010;**5**(8):e12149. DOI: 10.1371/journal.pone.0012149
- [18] Degli Esposti M, Chouaia B, Comandatore F, et al. Evolution of mitochondria reconstructed from the energy metabolism of living bacteria. *PLoS One*. 2014;**9**(5). DOI: e96566, 10.1371/journal.pone.0096566
- [19] Sagan L. On the origin of mitosing cells. *Journal of Theoretical Biology*. 1967;**14**(3):225-274
- [20] Gibson CM, Hunter MS. Extraordinarily widespread and fantastically complex: Comparative biology of endosymbiotic bacterial and fungal mutualists of insects. *Ecology Letters*. 2010;**13**(2):223-234. DOI: 10.1111/j.1461-0248.2009.01416.x
- [21] Mackiewicz P, Bodyl A, Gagat P. Possible import routes of proteins into the cyanobacterial endosymbionts/plastids of *Paulinella chromatophora*. *Theory in Biosciences*. 2012;**131**(1):1-18. DOI: 10.1007/s12064-011-0147-7
- [22] Lazcano A, Peretó J. On the origin of mitosing cells: A historical appraisal of Lynn Margulis endosymbiotic theory. *Journal of Theoretical Biology*. 2017;**434**:80-87. DOI: 10.1016/j.jtbi.2017.06.036
- [23] Neish AS. Microbes in gastrointestinal health and disease. *Gastroenterology*. 2009; **136**(1):65-80. DOI: 10.1053/j.gastro.2008.10.080
- [24] Yegani M, Korver D. Factors affecting intestinal health in poultry. *Poultry Science*. 2008;**87**(10):2052-2063. DOI: 10.3382/ps.2008-00091
- [25] Maslowski KM, Mackay CR. Diet, gut microbiota and immune responses. *Nature Immunology*. 2011;**12**(1):5-9. DOI: 10.1038/ni0111-5

- [26] Musso G, Gambino R, Cassader M. Obesity, diabetes, and gut microbiota: The hygiene hypothesis expanded? *Diabetes Care*. 2010;**33**(10):2277-2284. DOI: 10.2337/ dc10-0556
- [27] Schiffrin E, Blum S. Interactions between the microbiota and the intestinal mucosa. *European Journal of Clinical Nutrition*. 2002;**56**:S60-S64. DOI: 10.1038/sj.ejcn.1601489
- [28] Sharma R, Young C, Neu J. Molecular modulation of intestinal epithelial barrier: Contribution of microbiota. *Journal of Biomedicine & Biotechnology*. 2010;**30**:5879. DOI: 10.1155/2010/305879
- [29] Xu J, Gordon JL. Honor thy symbionts. *Proceedings of the National Academy of Sciences of the United States of America*. 2003;**100**(18):10452-10459. DOI: 10.1073/pnas.1734063100
- [30] Blaser MJ. Who are we? Indigenous microbes and the ecology of human diseases. *EMBO Reports*. 2006;**7**(10):956. DOI: 10.1038/sj.embor.7400812
- [31] Xu J, Mahowald MA, Ley RE, et al. Evolution of symbiotic bacteria in the distal human intestine. *PLoS Biology*. 2007;**5**(7):e156. DOI: 10.1371/journal.pbio.0050156
- [32] Fraune S, Bosch TC. Why bacteria matter in animal development and evolution. *BioEssays*. 2010;**32**(7):571-580. DOI: 10.1002/bies.200900192
- [33] Martin R, Nauta A, Ben Amor K, et al. Early life: Gut microbiota and immune development in infancy. *Beneficiary Microbes*. 2010;**1**(4):367-382. DOI: 10.3920/BM2010.0027
- [34] Sekirov I, Russell SL, Antunes LCM, et al. Gut microbiota in health and disease. *Physiological Reviews*. 2010;**90**(3):859-904. DOI: 10.1152/physrev.00045.2009
- [35] McFall-Ngai M. Adaptive immunity: Care for the community. *Nature*. 2007;**445**(7124):153. DOI: 10.1038/445153a
- [36] Duerkop BA, Vaishnava S, Hooper LV. Immune responses to the microbiota at the intestinal mucosal surface. *Immunity*. 2009;**31**(3):368-376. DOI: 10.1016/j.immuni.2009.08.009
- [37] Moran NA. Symbiosis as an adaptive process and source of phenotypic complexity. *Proceedings of the National Academy of Sciences of the United States of America*. 2007;**104**(Suppl 1):8627-8633. DOI: 10.1073/ pnas.0611659104
- [38] Sherman PM, Ossa JC, Johnson-Henry K. Unraveling mechanisms of action of probiotics. *Nutrition in Clinical Practice*. 2009;**24**(1):10-14. DOI: 10.1177/0884533608329231
- [39] Tlaskalová-Hogenová H, Stepánková R, Kozáková H, et al. The role of gut microbiota (commensal bacteria) and the mucosal barrier in the pathogenesis of inflammatory and autoimmune diseases and cancer: Contribution of germ-free and gnotobiotic animal models of human diseases. *Cellular & Molecular Immunology*. 2011;**8**(2):110-120. DOI: 10.1038/cmi.2010.67
- [40] Bergman E. Energy contributions of volatile fatty acids from the gastrointestinal tract in various species. *Physiological Reviews*. 1990;**70**(2):567-590. DOI: 10.1152/physrev.1990.70.2.567

- [41] Walter J, Britton RA, Roos S. Host-microbial symbiosis in the vertebrate gastrointestinal tract and the *Lactobacillus reuteri* paradigm. *Proceedings of the National Academy of Sciences of the United States of America*. 2011;**108**(Suppl 1):4645-4652. DOI: 10.1073/pnas.1000099107
- [42] Fuller R, Brooker B. Lactobacilli which attach to the crop epithelium of the fowl. *The American Journal of Clinical Nutrition*. 1974;**27**(11):1305-1312
- [43] Qiu R, Croom J, Ali R, et al. Direct fed microbial supplementation repartitions host energy to the immune system. *Journal of Animal Science*. 2012;**90**(8):2639-2651. DOI: 10.2527/jas.2011-4611
- [44] Tellez G, Higgins S, Donoghue A, et al. Digestive physiology and the role of micro-organisms. *Journal of Applied Poultry Research*. 2006;**15**(1):136-144. DOI: 10.1093/japr/15.1.136
- [45] Tellez G, Pixley C, Wolfenden R, et al. Probiotics/direct fed microbials for salmonella control in poultry. *Foodservice Research International*. 2012;**45**(2):628-633. DOI: 10.1016/j.foodres.2011.03.047
- [46] Dass N, John A, Bassil A, et al. The relationship between the effects of short-chain fatty acids on intestinal motility in vitro and GPR43 receptor activation. *Neurogastroenterology and Motility*. 2007;**19**(1):66-74. DOI: 10.1111/j.1365-2982.2006.00853.x
- [47] Dale C, Moran NA. Molecular interactions between bacterial symbionts and their hosts. *Cell*. 2006;**126**(3):453-465. DOI: 10.1016/j.cell.2006.07.014
- [48] Dethlefsen L, McFall-Ngai M, Relman DA. An ecological and evolutionary perspective on human-microbe mutualism and disease. *Nature*. 2007;**449**(7164):811-818. DOI: 10.1038/nature06245
- [49] Choct M. Managing gut health through nutrition. *British Poultry Science*. 2009;**50**(1):9-15. DOI: 10.1080/00071660802538632
- [50] Bäckhed F. Programming of host metabolism by the gut microbiota. *Annals of Nutrition & Metabolism*. 2011;**58**(Suppl 2):44-52. DOI: 10.1159/000328042
- [51] Kau AL, Ahern PP, Griffin NW, et al. Human nutrition, the gut microbiome and the immune system. *Nature*. 2011;**474**(7351):327-336. DOI: 10.1038/nature10213
- [52] Cani PD, Bibiloni R, Knauf C, et al. Changes in gut microbiota control metabolic endotoxemia-induced inflammation in high-fat diet-induced obesity and diabetes in mice. *Diabetes*. 2008;**57**(6):1470-1481. DOI: 10.2337/db07-1403
- [53] Cani PD, Delzenne NM. The role of the gut microbiota in energy metabolism and metabolic disease. *Current Pharmaceutical Design*. 2009;**15**(13):1546-1558. DOI: 10.2174/138161209788168164
- [54] Saleh M, Elson CO. Experimental inflammatory bowel disease: Insights into the host-microbiota dialog. *Immunity*. 2011;**34**(3):293-302. DOI: 10.1016/j.immuni.2011.03.008

- [55] Elson CO, Cong Y. Host-microbiota interactions in inflammatory bowel disease. *Gut Microbes*. 2012;**3**(4):332-344. DOI: 10.4161/gmic.20228
- [56] Shen J, Obin MS, Zhao L. The gut microbiota, obesity and insulin resistance. *Molecular Aspects of Medicine*. 2012;**34**(1):39-58. DOI: 10.2119/molmed.2012.00111
- [57] Tagliabue A, Elli M. The role of gut microbiota in human obesity: Recent findings and future perspectives. *Nutrition, Metabolism, and Cardiovascular Diseases*. 2012;**23**(3):160-168. DOI: 10.1016/j.numecd.2012.09.002
- [58] Salzman NH. Microbiota-immune system interaction: An uneasy alliance. *Current Opinion in Microbiology*. 2011;**14**(1):99-105. DOI: 10.1016/j.mib.2010.09.018
- [59] Di Mauro A, Neu J, Riezzo G, et al. Gastrointestinal function development and microbiota. *Italian Journal of Pediatrics*. 2013;**39**:15. DOI: 10.1186/1824-7288-39-15
- [60] Cario E. Innate immune signalling at intestinal mucosal surfaces: A fine line between host protection and destruction. *Current Opinion in Gastroenterology*. 2008;**24**(6):725-732. DOI: 10.1097/MOG.0b013e32830c4341
- [61] Sansonetti PJ. Host-bacteria homeostasis in the healthy and inflamed gut. *Current Opinion in Gastroenterology*. 2008;**24**(4):435-439. DOI: 10.1097/MOG.0b013e32830007f7
- [62] Feng T, Elson CO. Adaptive immunity in the host-microbiota dialog. *Mucosal Immunology*. 2011;**4**(1):15-21. DOI: 10.1038/mi.2010.60
- [63] Ohland CL, Jobin C. Microbial activities and intestinal homeostasis: A delicate balance between health and disease. *Cellular and Molecular Gastroenterology and Hepatology*. 2015;**1**(1):28-40. DOI: 10.1016/j.jcmgh.2014.11.004
- [64] Hooper LV, Macpherson AJ. Immune adaptations that maintain homeostasis with the intestinal microbiota. *Nature Reviews. Immunology*. 2010;**10**(3):159-169. DOI: 10.1038/nri2710
- [65] Mazmanian SK, Round JL, Kasper DL. A microbial symbiosis factor prevents intestinal inflammatory disease. *Nature*. 2008;**453**:620-625. DOI: 10.1038/nature07008
- [66] Albenberg LG, Wu GD. Diet and the intestinal microbiome: Associations, functions, and implications for health and disease. *Gastroenterology*. 2014;**146**(6):1564-1572. DOI: 10.1053/j.gastro.2014.01.058
- [67] Hamaker BR, Tuncil YE. A perspective on the complexity of dietary fiber structures and their potential effect on the gut microbiota. *Journal of Molecular Biology*. 2014;**426**(23):3838-3850
- [68] Sonnenburg ED, Sonnenburg JL. Starving our microbial self: The deleterious consequences of a diet deficient in microbiota-accessible carbohydrates. *Cell Metabolism*. 2014;**20**(5):779-786. DOI: 10.1016/j.cmet.2014.07.003
- [69] El Kaoutari A, Armougom F, Gordon JL, et al. The abundance and variety of carbohydrate-active enzymes in the human gut microbiota. *Nature Reviews. Microbiology*. 2013;**11**(7):497-504. DOI: 10.1038/nrmicro3050

- [70] De Filippo C, Cavalieri D, Di Paola M, et al. Impact of diet in shaping gut microbiota revealed by a comparative study in children from europe and rural africa. *Proceedings of the National Academy of Sciences of the United States of America*. 2010;**107**(33):14691-14696. DOI: 10.1073/pnas.1005963107
- [71] Yatsunencko T, Rey FE, Manary MJ, et al. Human gut microbiome viewed across age and geography. *Nature*. 2012;**486**:222-227. DOI: 10.1038/nature11053
- [72] Schnorr SL, Candela M, Rampelli S, et al. Gut microbiome of the hadza hunter-gatherers. *Nature Communications*. 2014;**5**:3654. DOI: 10.1038/ncomms4654
- [73] Sonnenburg ED, Smits SA, Tikhonov M, et al. Diet-induced extinctions in the gut microbiota compound over generations. *Nature*. 2016;**529**:212-215. DOI: 10.1038/nature16504
- [74] Kim J-Y, Kwon YM, Kim I-S, et al. Effects of the Brown seaweed *Laminaria japonica* supplementation on serum concentrations of IgG, triglycerides, and cholesterol, and intestinal microbiota composition in rats. *Frontiers in Nutrition*. 2018;**5**:23. DOI: 10.3389/fnut.2018.00023
- [75] Daien CI, Pinget GV, tan JK, et al. detrimental impact of microbiota-accessible carbohydrate-deprived diet on gut and immune homeostasis: An overview. *Frontiers in Immunology*. 2017;**8**:548. DOI: 10.3389/fimmu.2017.00548
- [76] Nealson KH, Platt T, Hastings JW. Cellular control of the synthesis and activity of the bacterial luminescent system. *Journal of Bacteriology*. 1970;**104**(1):313-322
- [77] Nealson KH, Hastings JW. Bacterial bioluminescence: Its control and ecological significance. *Microbiological Reviews*. 1979;**43**(4):496-518
- [78] Fuqua C, Winans SC, Greenberg EP. Census and consensus in bacterial ecosystems: The LuxR-LuxI family of quorum-sensing transcriptional regulators. *Annual Reviews in Microbiology*. 1996;**50**(1):727-751. DOI: 10.1146/annurev.micro.50.1.727
- [79] Telford G, Wheeler D, Williams P, et al. The pseudomonas aeruginosa quorum-sensing signal molecule N-(3-oxododecanoyl)-L-homoserine lactone has immunomodulatory activity. *Infection and Immunity*. 1998;**66**(1):36-42
- [80] Sperandio V, Torres AG, Jarvis B, et al. Bacteria-host communication: The language of hormones. *Proceedings of the National Academy of Sciences of the United States of America*. 2003;**100**(15):8951-8956. DOI: 10.1073/pnas.1537100100
- [81] Havarstein LS, Coomaraswamy G, Morrison DA. An unmodified heptadecapeptide pheromone induces competence for genetic transformation in streptococcus pneumoniae. *Proceedings of the National Academy of Sciences of the United States of America*. 1995;**92**(24):11140-11144
- [82] Magnuson R, Solomon J, Grossman AD. Biochemical and genetic characterization of a competence pheromone from *B. subtilis*. *Cell*. 1994;**77**(2):207-216
- [83] Solomon JM, Lazazzera BA, Grossman AD. Purification and characterization of an extracellular peptide factor that affects two different developmental pathways in bacillus subtilis. *Genes & Development*. 1996;**10**(16):2014-2024

- [84] Mayville P, Ji G, Beavis R, et al. Structure-activity analysis of synthetic autoinducing thiolactone peptides from staphylococcus aureus responsible for virulence. *Proceedings of the National Academy of Sciences of the United States of America*. 1999;**96**(4):1218-1223
- [85] Ng W, Bassler BL. Bacterial quorum-sensing network architectures. *Annual Review of Genetics*. 2009;**43**:197-222. DOI: 10.1146/annurev-genet-102108-134304
- [86] Monnet V, Gardan R. Quorum-sensing regulators in Gram-positive bacteria: 'cherchez le peptide'. *Molecular Microbiology*. 2015;**97**(2):181-184. DOI: 10.1111/mmi.13060
- [87] Rutherford ST, Bassler BL. Bacterial *quorum sensing*: Its role in virulence and possibilities for its control. *Cold Spring Harbor Perspectives in Medicine*. 2012;**2**(11):a012427. DOI: 10.1101/cshperspect.a012427
- [88] Sun W, Cao JG, Teng K, et al. Biosynthesis of poly-3-hydroxybutyrate in the luminescent bacterium, vibrio harveyi, and regulation by the lux autoinducer, N-(3-hydroxybutanoyl) homoserine lactone. *The Journal of Biological Chemistry*. 1994;**269**(32):20785-20790
- [89] Wei Y, Perez LJ, Ng W, et al. Mechanism of vibrio cholerae autoinducer-1 biosynthesis. *ACS Chemical Biology*. 2011;**6**(4):356-365. DOI: 10.1021/cb1003652
- [90] Engebrecht J, Nealson K, Silverman M. Bacterial bioluminescence: Isolation and genetic analysis of functions from vibrio fischeri. *Cell*. 1983;**32**(3):773-781
- [91] Hughes DT, Sperandio V. Inter-kingdom signalling: Communication between bacteria and their hosts. *Nature Reviews. Microbiology*. 2008;**6**:111-120. DOI: 10.1038/nrmicro-1836
- [92] Kendall MM, Sperandio V. What a dinner party! Mechanisms and functions of interkingdom signaling in host-pathogen associations. *MBio*. 2016;**7**(2):e01748-15. DOI: 10.1128/mBio.01748-15
- [93] Knoll AT, Carlezon WA. Dynorphin, stress, and depression. *Brain Research*. 2010; **1314C**:56. DOI: 10.1016/j.brainres.2009.09.074
- [94] Felli C, Vincentini O, Silano M, et al. HIV-1 nef signaling in intestinal mucosa epithelium suggests the existence of an active inter-kingdom crosstalk mediated by exosomes. *Frontiers in Microbiology*. 2017;**8**:1022. DOI: 10.3389/fmicb.2017.01022
- [95] Williams MR, Stedtfeld RD, Tiedje JM, et al. MicroRNAs-based inter-domain communication between the host and members of the gut microbiome. *Frontiers in Microbiology*. 2017;**8**:1896. DOI: 10.3389/fmicb.2017.01896
- [96] Zhou G, Zhou Y, Chen X. New insight into inter-kingdom communication: Horizontal transfer of mobile small RNAs. *Frontiers in Microbiology*. 2017;**8**:768. DOI: 10.3389/fmicb.2017.00768
- [97] McFall-Ngai MJ. Unseen forces: The influence of bacteria on animal development. *Developmental Biology*. 2002;**242**(1):1-14. DOI: 10.1006/dbio.2001.0522
- [98] Bercik P, Denou E, Collins J, et al. The intestinal microbiota affect central levels of brain-derived neurotropic factor and behavior in mice. *Gastroenterology*. 2011;**141**(2):599-609. DOI: 10.1053/j.gastro.2011.04.052

- [99] Bercik P, Park A, Sinclair D, et al. The anxiolytic effect of *Bifidobacterium longum* NCC3001 involves vagal pathways for gut-brain communication. *Neurogastroenterology and Motility*. 2011;**23**(12):1132-1139. DOI: 10.1111/j.1365-2982.2011.01796.x
- [100] Lyte M. Probiotics function mechanistically as delivery vehicles for neuroactive compounds: Microbial endocrinology in the design and use of probiotics. *BioEssays*. 2011;**33**(8):574-581. DOI: 10.1002/bies.201100024
- [101] Iyer LM, Aravind L, Coon SL, et al. Evolution of cell-cell signaling in animals: Did late horizontal gene transfer from bacteria have a role? *Trends in Genetics*. 2004;**20**(7):292-299. DOI: 10.1016/j.tig.2004.05.007
- [102] Ratcliffe EM, Farrar NR, Fox EA. Development of the vagal innervation of the gut: Steering the wandering nerve. *Neurogastroenterology and Motility*. 2011;**23**(10):898-911. DOI: 10.1111/j.1365-2982.2011.01764.x
- [103] Lallès J-P, Bosi P, Smidt H, et al. Nutritional management of gut health in pigs around weaning. *The Proceedings of the Nutrition Society*. 2007;**66**(2):260-268. DOI: 10.1017/S0029665107005484
- [104] Aly SM, Abdel-Galil Ahmed Y, Abdel-Aziz Ghareeb A, et al. Studies on *Bacillus subtilis* and *Lactobacillus acidophilus*, as potential probiotics, on the immune response and resistance of *Tilapia nilotica* (*Oreochromis niloticus*) to challenge infections. *Fish & Shellfish Immunology*. 2008;**25**(1-2):128-136. DOI: 10.1016/j.fsi.2008.03.013
- [105] Konturek P, Brzozowski T, Konturek S. Stress and the gut: Pathophysiology, clinical consequences, diagnostic approach and treatment options. *Journal of Physiology and Pharmacology*. 2011;**62**(6):591-599
- [106] MacFabe DF. Short-chain fatty acid fermentation products of the gut microbiome: Implications in autism spectrum disorders. *Microbial Ecology in Health and Disease*. 2012;**23**:19260. DOI: 10.3402/mehd.v23i0.19260
- [107] Midtvedt T. The gut: A triggering place for autism-possibilities and challenges. *Microbial Ecology in Health and Disease*. 2012;**23**:18982. DOI: 10.3402/mehd.v23i0.18982
- [108] Kang D-W, Park JG, Ilhan ZE, et al. Reduced incidence of *Prevotella* and other fermenters in intestinal microflora of autistic children. *PLoS One*. 2013;**8**:e68322. DOI: 10.1371/journal.pone.0068322
- [109] Wang L, Christophersen CT, Sorich MJ, et al. Increased abundance of *Sutterella* spp. and *Ruminococcus torques* in feces of children with autism spectrum disorder. *Molecular Autism*. 2013;**4**:42. DOI: 10.1186/2040-2392-4-42
- [110] Goossens D, Jonkers D, Stobberingh E, et al. Probiotics in gastroenterology: Indications and future perspectives. *Scandinavian Journal of Gastroenterology Supplement*. 2003;**239**:15-23
- [111] Elson CO, Cong Y, Qi F, et al. Molecular approaches to the role of the microbiota in inflammatory bowel disease. *Annals of the New York Academy of Sciences*. 2006;**1072**:39-51. DOI: 10.1196/annals.1326.010

- [112] Wu H-J, Wu E. The role of gut microbiota in immune homeostasis and autoimmunity. *Gut Microbes*. 2012;**3**(1):4-14. DOI: 10.4161/gmic.19320
- [113] Liu WH, Chuang HL, Huang YT, et al. Alteration of behavior and monoamine levels attributable to *Lactobacillus plantarum* PS128 in germ-free mice. *Behavioural Brain Research*. 2016;**298**(Pt B):202-209. DOI: 10.1016/j.bbr.2015.10.046
- [114] Karavolos MH, Spencer H, Bulmer D, et al. Adrenaline modulates the global transcriptional profile of *Salmonella* revealing a role in the antimicrobial peptide and oxidative stress resistance responses. *BMC Genomics*. 2008;**9**:458. DOI: 10.1186/1471-2164-9-458
- [115] Karavolos MH, Bulmer DM, Spencer H, et al. *Salmonella* Typhi sense host neuroendocrine stress hormones and release the toxin haemolysin E. *EMBO Reports*. 2011;**12**(3):252-258. DOI: 10.1038/embor.2011.4
- [116] Moreira CG, Weinshenker D, Sperandio V. QseC mediates *Salmonella enterica* serovar Typhimurium virulence in vitro and in vivo. *Infection and Immunity*. 2010;**78**(3):914-926. DOI: 10.1128/IAI.01038-09
- [117] Moreira CG, Sperandio V. Interplay between the QseC and QseE bacterial adrenergic sensor kinases in *Salmonella enterica* serovar Typhimurium pathogenesis. *Infection and Immunity*. 2012;**80**(12):4344-4353. DOI: 10.1128/IAI.00803-12
- [118] Foster JA, Linda R, Cryan JF. Stress & the gut-brain axis: Regulation by the microbiome. *Neurobiology of Stress*. 2017;**7**:124-136. DOI: <https://doi.org/10.1016/j.ynstr.2017.03.001>
- [119] Sandhu KV, Sherwin E, Schellekens H, et al. Feeding the microbiota-gut-brain axis: Diet, microbiome, and neuropsychiatry. *Translational Research*. 2017;**179**:223-244. DOI: <https://doi.org/10.1016/j.trsl.2016.10.002>
- [120] Perez-Muñoz ME, Arrieta M, Ramer-Tait AE, et al. A critical assessment of the “sterile womb” and “in utero colonization” hypotheses: Implications for research on the pioneer infant microbiome. *Microbiome*. 2017;**5**(1):48
- [121] Tiihonen K, Ouwehand AC, Rautonen N. Human intestinal microbiota and healthy ageing. *Ageing Research Reviews*. 2010;**9**(2):107-116. DOI: 10.1016/j.arr.2009.10.004
- [122] Dicks L, Geldenhuys J, Mikkelsen L, et al. Our gut microbiota: A long walk to homeostasis. *Beneficial Microbes*. 2018;**9**:3-20. DOI: 10.3920/BM2017.0066