Chapter 1

Prokaryotes Rule the World

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http://dx.doi.org/10.5772/intechopen.77953

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

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

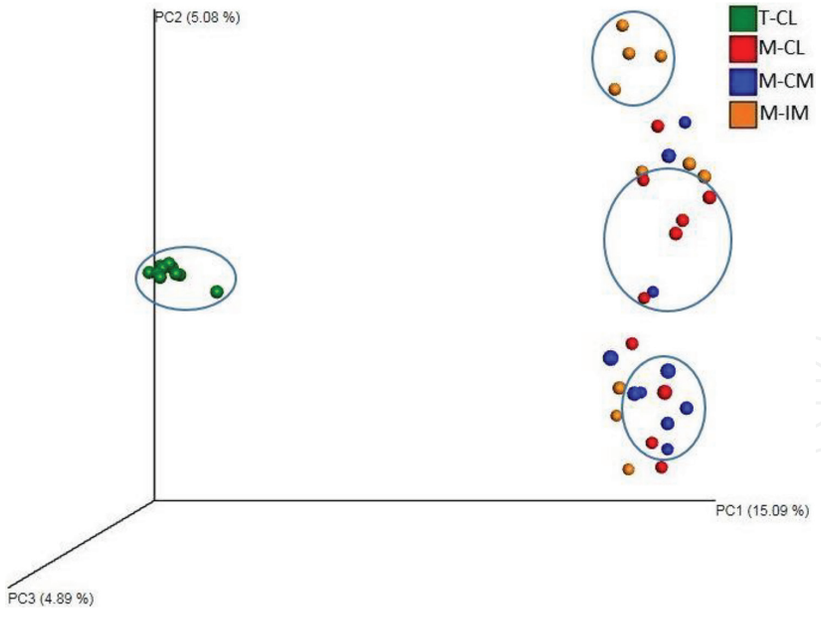

Figure 1. PCoA plot showing significant difference in bacterial community structure among different regions and locations of gastrointestinal tract of 3-week old chickens. MRS-recovered cells from cecal lumen (M-CL), cecal mucosa (M-CM) and ileal mucosa (M-IM), and total bacterial cells from cecal lumen (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 ~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 concretion, 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 synthesize 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 though *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 homoeostasis 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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