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Food & Nutrition Journal

Mini Review

Adhikari B, et al. Food Nutr J 3: 170.
DOI: 10.29011/2575-7091.100070

How Trillions of Microbes Residing on Gastrointestinal Tract Maintain Homeostasis with Host Cells?

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Citation: Adhikari B, Kwon YM, Hargis BM and Tellez G (2018) How Trillions of Microbes Residing on Gastrointestinal Tract Maintain Homeostasis with Host Cells?. Food Nutr J 3: 170. DOI: 10.29011/2575-7091.100070

Received Date: 03 March, 2018; **Accepted Date:** 14 March, 2018; **Published Date:** 22 March, 2018

Abstract

Trillions of microbes reside on our gut which are so diverse and complex. Our understanding of their composition, structure, and various roles in health and diseases have been increasing day by day along with the advancement in sequencing technologies and computational methods. It is very important to maintain microbial homeostasis inside gut because dysbiosis has been associated with various diseases and disorders including allergies, inflammatory bowel disease, diabetes, cancer, and autism. Proper understanding of various mechanisms involved in gut microbial homoestasis is crucial to modulate their composition or treat diseases. Albeit very little is known about possible mechanisms involved in gut microbial homeostasis, different microbial activities including co-operation (biofilm formation, horizontal gene transfer, quorum sensing etc.), competition, and combation, and host responses of their immune system, gut barrier function and different dietary components are some of the key factors that can affect on gut homeostasis. The objective of this review is to point out different factors involved in gut microbial homeostasis with emphasis on host intestinal barrier and immune system, dietary components and Quorum sensing.

Keywords: Digestive Physiology; Eukaryotes; Microbiome; Prokaryotes; Quorum Sensing

Background

Almost any metazoan, either invertebrates or vertebrates harbor gut microbiota [1]. Previously, around 1014 bacteria was estimated to be present in the alimentary tract of the human [2], and the ratio of total microbiome to the total number of somatic and germ cells present in human was estimated to be 10:1. However, a recent study shows the variations in gut bacterial number from 107 (Stomach, Duodenum, and Jejunum) to 1014 (Colon), and estimates the ratio of total bacteria to total number of human cells as ~1:1 [3]. The human genome contains around 20,000 genes [4] whereas around 3.3 million non-redundant genes are found to be present in microbiome of gastrointestinal tract. More than 99% of these genes belong to 1000 to 1150 different bacterial species [5] representing diverse and complex human gut microbiota.

Along with the advancement in sequencing technologies, tremendous efforts have made in characterizing compositions and functions of microbiota, and have reported diverse groups of microbiota residing in various regions of hosts such as, skin, oral cavity, nasal cavity, urogenital tract, and gut [5,6]. It is now widely accepted that the composition of microbiota not only vary with different segments of gut but also with different locations (lumen vs. mucosa) within the same segment [7-9]. Microbiota (especially bacteria) residing in gastrointestinal tract have been widely studied and have been found to affect on health and diseases through complex interactions with their hosts including humans and animals. Different factors including diets, antibiotics, method of delivery and infant feeding, illness, stress, aging, lifestyles, and host genetics have been found to affect on gut microbiota [10,11]. It is very important to have a balance gut microbiota in order to maintain health and homeostasis. Changes in gut microbiota compositions (dysbiosis) due to any factors as described above can cause several diseases and disorders including allergies, Inflammatory Bowel Disease (IBD), diabetes, cancer, and autism as reviewed earlier [10]. Although detail mechanisms that are responsible for maintaining gut microbial homoeostasis need to be explored more in the future, some of the key mechanisms identified and studies so far are described below:

Intestinal Barrier and Host Immune System for Maintaining Homoeostasis

Various activities are required for maintaining homoeostasis of bacteria in gut. Intestinal immune system and gut barrier function of the host play an important role in microbiota composition and stability. Dietary antigens, toxic compounds, or pathogenic organisms which are in continuous contact with epithelial cells trigger host immune system causing inflammation as a protective response [12,13]. Although inflammation is a protective response to infection or tissue injury, long-term or chronic inflammation can results serious outcomes like IBD [14]. Thus, the host immune system has to be adapted in such a way that it can tolerant commensal bacteria, but recognize and destroy pathogenic or opportunistic commensal organisms. Such type of immune tolerance can be achieved directly through Microbe-Associated Molecular Pattern (MAMP) or polysaccharide A (PSA) signaling [15].

The host's intestinal epithelial cells provide different barriers to pathogenic bacteria including production of mucus from goblet cells, secretion of antimicrobial peptides from Paneth cells, IgA from plasma cells, forming intercellular tight junction complexes, and recognition of MAMP [15,16]. Beside these, certain products from symbionts can prevent colonization of pathogenic or opportunistic commensal bacteria. For example, a single microbial molecule (PSA) synthesized by Bacteroides fragilis was found to protect from colitis induced by *Helicobacter hepaticus* through suppression of pro-inflammatory interleukin-17 and promotion of interleukin-10-producing CD4+ T cells [17]. Similarly, commensal bacteria can invade into epithelial cells of host to activate innate and adaptive immune system which can eliminate pathogens [16]. Moreover, commensal bacteria promote lipopolysaccharides (LPS) detoxification through the activation of epithelial intestinal alkaline phosphatase (IAP) expression and also involve in gut-associated lymphoid tissue (GALT) development and secondary bile acids formation [15].

Role of Different Dietary Components for Maintaining Homoestasis

Various dietary components including carbohydrates, protein, and fat serve as sources of microbial metabolism and affect greatly on structure, composition, and diversities of microbiota which have been reviewed elsewhere [18,19]. Among different sources of carbohydrates that are utilized by gut microbe for fermentation, dietary fiber is the most common source of fuel for human microbes [20]. Dietary fibers are complex carbohydrates of plant origin that cannot be digested by host itself and need certain enzymes synthesized by gut bacteria for digestion [21]. Western diets are lower in dietary fibers as compared to traditional diets and these differences have significant impact on microbiota composition and diversity. Changes in microbiota composition, reduced microbial diversity and lower production of Short Chain Fatty Acids (SCFA) have been reported in individuals having Western diet compared to traditional diet [22-24]. Recently, those carbohydrates that can be metabolically utilized by gut microbes has been termed as "microbiota-accessible carbohydrates" (MACs) which affect on microbial composition, their functions and metabolic activities [20]. A recent study reported progressive loss of microbial diversity in mice fed with low dietary MACs which were recoverable with in the same generation by supplementating higher MACs, however, were irrecoverable in second, third, and fourth generation though supplied with higher MACs [25]. In addition, MAC deprived diet can have detrimental impact on gut microbiota homeostasis that can provoke the development of different inflammatory diseases including allergies, infections, and autoimmune diseases as reviewed earlier [26].

Short Chain Fatty Acids (SCFA) such as, acetate, propionate, and butyrate that are produced through fermentation of carbohydrates by enteric microbiota play an important role in maintaining homoestasis of gut microbiota. SCFA play a vital role in various activities including induction of IgA, secretion of mucous, and promotion of intestinal barrier, beside immune tolerance to commensal bacteria through indirectly regulation of B and T cells [15].

Interactions Between Microbes and their Roles in Maintaining Microbial Homoestasis

Complex microbial interactions through their communication systems which help to communicate between themselves or with hosts help them to maintain their niches and host homoestasis. Microbial interactions can be either mutualistic or antagonistic and thus either they co-operate each other through horizontal gene transfer, biofilm formation, and quorum sensing or compete for nutrients and combat with other species or pathogens through expression of bacteriocins, microcins, and colicins [15].

Interkingdom Communication: Communication Between Microbes and Hosts

Communication/signaling between bacteria and hosts is known as interkingdom communication. Communication between bacteria was first described in two marine bioluminescent bacteria, Vibrio fischeri and Vibrio harveyi as an autoinduction [27,28] which was later termed as Quorum Sensing (QS) [29]. Quorum sensing is a process of cell to cell communication between bacteria which enables them to gather information regarding changes in population density and alter genes expression accordingly. The process of QS involves production, detection and response to extra-cellular signaling molecules known as Auto Inducers (AIs). Increase concentration of AIs as a result of increase population density help bacteria to monitor changes in their cell numbers and response collectively by altering genes expression globally. Previously, QS was believed to occur only among bacteria, but later on, several studies reported the existence of cross communication

between bacterial and host signaling system [30,31].

QS in Gram-positive and Gram-negative Bacteria

It is now established fact that both Gram-positive and Gram-negative bacteria use QS. There exist differences not only in AIs they detect, but also in the mechanism how they response to different AIs. In Gram-positive bacteria, secreted peptides serve as signaling molecule. Peptides which are synthesized inside bacterial cells undergo some modifications through processing and cyclization during the process of secretion fascinated with specialized transporters [32-36]. Once secreted peptides reach to a threshold concretion, they are detected at the bacterial surface by the sensor protein which enable bacterial cells to modulate gene expression at a population level [37]. Specifically, when concentration of secreted peptides reach high in response to high population density, they bind to membrane-bound histidine kinase receptor that activates its kinase activity leading to autophosphorylation and phosphorylation of cytoplasmic response regulator. The phosphorylated cytoplasmic response regulator leads to the activation of genes expression in the QS regulon. In addition to this, secreted peptides can be directly transported back to the cytoplasm of the cell where they can alter gene expression by interacting with the transcription factors [38]. In sum, QS in Gram-positive bacteria occur by using secreted peptides through two component system, that consists of membrane-bound histidine kinase receptor and a transcription regulating cognate cytoplasmic response regulator.

Gram negative bacteria typically use acyl-homoserine lactones (AHLs) as an autoinducer in QS [39]. In addition to this, they can use other signaling molecules like AI-2 and CAI-1 whose production is mainly dependent on S-adenosylmethionine (SAM) as a substrate [40]. LuxI/LuxR regulatory system of V. fischeri is a typical example of QS in Gram negative bacteria [41]. 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 receptors are cytoplasmic receptors whereas membrane bounds in case of Gram positive bacteria. Similarly, the AIs in case of Gram negative bacteria can freely diffuse in and out of the cell whereas they need to be transported in Gram positive bacteria.

Communication Between Bacteria and Hosts

Communication between bacteria and hosts involves hormones produced by host and hormones like chemicals i.e autoinducers (AIs) produced by bacteria [42]. 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 major hormones which are secreted as prohormones and transported out of the cell after processing. Protein or peptides hormones such as, Epidermal Growth Factor (EGF), insulin, glucagon etc. and amine hormones such as, catecholamines, adrenaline, noradrenaline (NA), dopamine etc. are some of the important hosts' hormones involved in interkingdom signaling [43].

Presence of specific bacterial receptors of those hormones produced by mammalian cells is 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 [43], adrenaline and nor adrenaline (A and NA) secreted by mammalian cells are sensed by bacterial membrane bound histidine kinases (QseC and QseE). In addition, QseC and QseE sense bacterial AI-3 signaling and sources of suphates (SO4) and phosphates (PO4), respectively. These signaling phosphorylate KdpE, QseB, and/or QseF that leads to activate the expression of T3SS, motility, and Shiga toxin. Dynorphin which is an important neuropeptide involved in the stress signal [44] has found to enter into bacterial cells and sensed by MvfR/PqsR receptor leading to increase in virulence of bacteria through quorum sensing, though 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 affect on LuxR-type regulators that inhibits 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 host's hormones are sensed by bacteria for manifestation of certain phenotypes. Gastrin, which is a peptide hormone secreted by stomach cells stimulates secretion of gastric acid and has been associated with increase in the growth of *H. pylori*. In addition, *H. pylori* infection has been found to associate with increase in gastrin secretion suggesting the interkingdom communication [43]. Other examples includes sensing of EGFs, opoid hormones etc.

Besides hormones, different nutrients such as, ethanolamine (EA) and sugars have also been reported to involve in QS. In addition, bacteria can sense different components of immune system such as, cytokines, apolipoprotein B (ApoB), Nox2, and antimicrobial peptides, modulating the host immune responses [43]. 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 [45]. Likewise, QS can occur not only with mammalian hosts but also with nonmammalian hosts including fish, insects, and plants as reviewed earlier [43]. 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 [46,47].

Summary

Although there is still debate regarding whether microbiota start colonization before or after birth of individuals [48], it has been widely accepted that methods of delivery affect on infants microbiota. Microbiota of infants are less diverse and are not stable initially which changes along with their growth. Once grown up, adult has a common core microbiota [49] which may change due to various factors including diets, medication, stress, genetics etc. as described above. Gut microbial homoestasis is very important for maintaining health of individuals which can be achieved by maintaining balance between pro- and inflammatory cytokines [50]. Although very little is known about how homoestasis is created by trillion of bacteria cells with host cells, different microbial activities including co-operation (biofilm formation, horizontal gene transfer, quorum sensing etc.), competition, and combation, and host responses of their immune system, gut barrier function and different dietary components are some of the key elements responsible for maintaining homoestasis in the gut. Communication between bacteria/virus and hosts (mammalian or nonmammalian) can occur through involvement of hormones and other different signaling molecules as described above. Such communications are expected to be common in different microbes including pathogens, and are involved in health and diseases of hosts through different activities such as, altering the virulence and modulating the host immune responses. Further explorations of various mechanisms involved in communication between microbes and host epithelial cells that stimulate production of different chemical substances including antimicrobial peptides, defensins etc. is needed for better understanding of gut microbial homoestasis.

Conflict of Interest

Authors declare no conflict of interest exist.

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