Chapter

Gut Microbiome: A New Organ System in Body

Haseeb Anwar, Shahzad Irfan, Ghulam Hussain, Muhammad Naeem Faisal, Humaira Muzaffar, Imtiaz Mustafa, Imran Mukhtar, Saima Malik and Muhammad Irfan Ullah

Abstract

The gut microbiome is comprised of various types of bacteria, fungi, protozoa, and viruses naturally occurring in humans and animals as normal microflora. Gut microorganisms are typically host specific, and their number and type vary according to different host species and environment. Gut microbes contribute directly and/or indirectly to various physiological processes including immune modulation, regulation of various neurotransmitter, and hormones, as well as production of many antioxidants and metabolites. They also play a role as antibiotic, anti-inflammatory, anti-diabetic, and anti-carcinogenic agents. Moreover, the ability of gut microbes to attenuate various systemic diseases like coronary heart disease, irritable bowel syndrome, metabolic diseases like diabetes mellitus, and infectious diseases like diarrhea has recently been reported. Current research findings have enough evidence to suggest that gut microbiome is a new organ system mainly due to the microorganisms' specific biochemical interaction with their hosts and their systemic integration into the host biology. Investigations into the potential ability of gut microbiome to influence metabolism inside their host via biochemical interaction with antibiotics and other drugs has recently been initiated. This chapter specifically focuses on the importance of gut microorganisms as a new organ system.

Keywords: gut microbiota, probiotics, metabolic disorders, gut health, drug metabolism

1. Introduction

Certain microorganisms have the unique ability to populate the human gastrointestinal tract and thus generally referred as gut microbiota. Gut microbiota is always non-pathological, and hence, the immune system is not triggered because of their presence. Humans co-evolved with a huge number of intestinal microbial species that offer to the host certain benefits by playing an important role in preventing them from pathogenic activities [1]. In addition to metabolic benefits, symbiotic bacteria benefit the host with various functions like boosting the immune homeostasis and inhibiting the colonization by other pathogenic microorganisms. The ability of symbiotic bacteria to inhibit pathogen colonization particularly in the gut is mediated

via several mechanisms including direct killing of pathogen, competition for limited nutrients, and enhancement of immune responses [2]. The intestinal microorganisms also co-evolved and have strong affiliations and association towards each other. In this evolutionary process, the persistent and enduring members of this microflora become more competent during unsettling influences and thereby become essential for human health [3]. Definite composition of human microbiome varies between individuals [4] particularly among lean and obese people. The microbiome is also affected by the dietary modifications adapted for the weight loss [5]. Examination of metabolic profiles of human infant microbiota revealed that ingestion, storage and digestion of dietary lipids were explicitly regulated by the microbiome [6, 7].

The human gut microbial communities are a mixture of microorganisms. The classes of microbes that constitute the gut microbiome communities differ between hosts. The difference is attributed to factors such as, inability of a microorganism to migrate between different hosts, intense environmental conditions inside and outside host's gut and host inconsistency in terms of genotype, diet, and colonization history [8]. The co-evolution of humans and their symbiotic microorganism has created bilateral interactions which are important for the health of humans, and any genetic or ecological change in this bilateral interaction can result in pathological conditions like infection [8]. Gut microbial communities are important for diverse host functions, including metabolism, fertility, development, immunity, and even antioxidant activities which promote health and fitness of the host [9–12]. The gut microbiome has a much larger genetic variety compared to the genome of the host, e.g., human genome is comprised of 20-25,000 genes whereas microbiome inhabiting the body is estimated to be in trillions. Almost 10^{10} microorganisms enter the human body daily and with the progress of co-evolution of gut microbes in humans, the capability of microbes to exchange their genes and associated functions with the environment are some of the main factors leading to host adaptation. Therefore, the "hologenome" model appraises the host and its microbes genomes as one unit under assortment [13, 14]. It is acknowledged that host-symbiont co-evolution is accountable for basic biological aspects.
In this chapter we aim to discuss the importance of gut microbiomes as a new organ system because of its association with the genetics and its role in the disease and health condition of the host. Moreover, the involvement of these microbiomes in shaping the overall health and constructing a symbiotic relationship with their host species is discussed as well as the co-evolution of gut microbes with the human body.

2. Inheritance of microbiome

2.1 Microbiome

A microbiome is the community of microbes dwelling collectively in a selected habitat. Humans, animals, vegetation, soils, oceans or even buildings have their own specific microbiome [15].

2.2 Host genetics and gut microbiome

The human gut environment is extremely complex with a unique ecology which comprises of trillion of microbiota with approximately 1.5 kg in mass. By using genetic techniques like 16S sequencing, 1000 microorganisms have been identified within the gut, with approx. 200 (0.5%) defining the core of the intestine microbiome [16]. These bacteria protect the gut epithelial cells against external pathogens. They also help the breakdown of indigestible dietary polysaccharides in the gut and

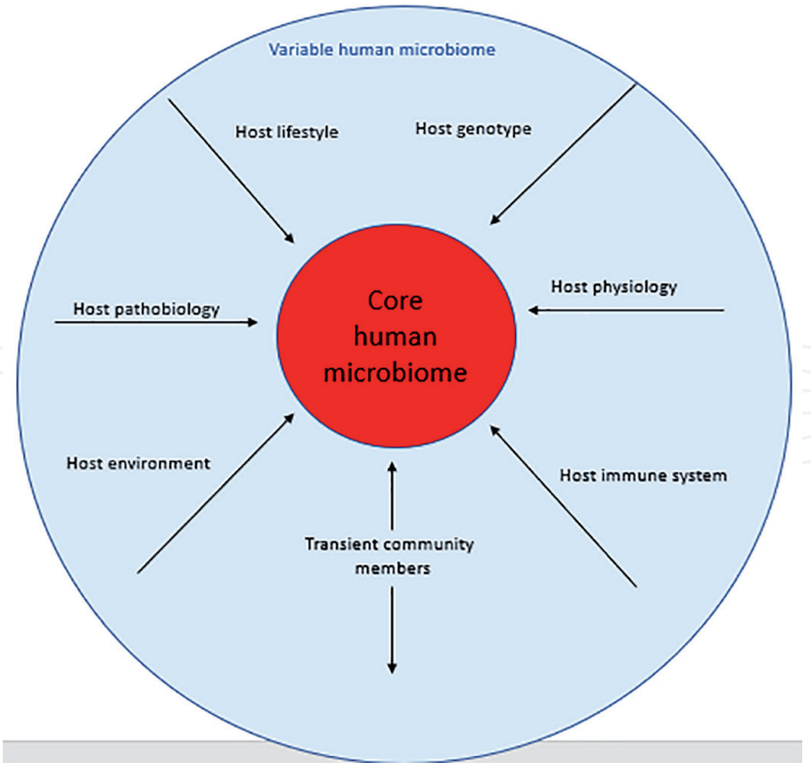

Figure 1.
Core human microbiome.

thus supply a quick chain of fatty acids, including acetate, butyrate, and propionate, which serve as vital metabolites for direct energy source of intestinal epithelial cells, prevention of insulin resistance and modulators of insulin secretion [17] (**Figure 1**).

The genetic makeup of humans is virtually identical, yet the small differences in DNA give rise to remarkable phenotypic assortment across the human population. The trillions of microbes inhabit our bodies and create complex, body-habitat-specific, adaptive ecosystems that are finely tuned to frequently changing host physiology [18]. A healthy "functional core" is actually a complement of metabolic and other molecular functions that are performed by the microbiome within a particular habitat but are not necessarily provided by the same organisms in different people [19].

2.3 Inherited microbiomes

The gastrointestinal tract (GIT) of humans is colonized by a vast variety of microbial population that can be understood as a complex and polygenetic trait which has been interacting and co-evolved with their host genetic environment [20–22]. It was previously considered that fetus lives in a germ free environment in the mother womb and the gut microbiota are transferred to the baby from mother's birth canal and body via horizontal transmission only [23]. But advanced researches have revealed that microbiota are also vertically transmitted to the infants from their mothers [24]. Presence of microbes in the meconium of the babies born by cesarean section clearly demonstrates that the gut microbes are not only derived after the birth [25, 26]. Moreover, presence of many microbes in the umbilical cord blood of the preterm babies and in the amniotic fluid substantiate the findings that the fetus in the mother womb is not totally sterile [27, 28]. Many gut bacterial genera are shared among the mammal species. The microbiomes of mice show strong fidelity throughout the generations and reiterate the intrinsic significance of these microorganisms in health.

2.4 Relationship of environment in shaping the microbiome

As mentioned above human intestinal microbiome composition is shaped by multiple factors like genetics, diet, environment and lifestyle. Several studies point towards stronger contribution by the environmental factors in shaping the gut microbial composition compared to the genetic factor [29]. It has also been speculated that gut microbial diversity affects the prediction accuracy for certain human traits including glucose and obesity problems, as compared to different animal models that use only host genetic and environmental factors [30].

2.5 Co-evolution and co-differentiation of host microbe interaction in exploring new drug targets

Horizontal gene transfer (HGT), genomic and metagenomics are possible approaches to identify drug targets that may also be considered as an evidence of co-evolution of hosts and their symbionts. Symbionts have the capacity to perform many metabolic activities including fermentation of dietary carbohydrates, drug metabolism, antimicrobial protection and immunomodulation, which is primarily due to the presence of genes in their genome which are missing in mammalian genomes. Therefore, horizontal gene transfer mechanisms are potential targets for drug discovery that become more evident with the use of gnotobiotics (germ free animal) in experimental trial to unveil the microbial function in the complex GIT microenvironment, and to investigate how orally administered drugs impact the gut microbial ecology in long term. HGT has gained immense interest in medical field as it contributes to the spreading of antibiotic resistance genes as well as it may cause closely related microbial strains to differ drastically in terms of clinical parameters [31]. Genetic variation in intestinal microbes may trigger the production of metabolites, but it may also generate changes in host's genome that may increase metabolite uptake or prevent their further synthesis. Co-evolution may lead to co-differentiation since permanent association of host and symbiont lineage can result in diversification [32]. The co-differentiation correlate resemblances in the microbial symbiont and the host [33, 34] which can be extended to an entire microbial community that passes vertically from host to offspring. Over the course of speciation, the microbial communities differentiate as a mirror to host phylogeny (such situation would be expected in hosts where parents immunize their offspring with microbial clique, e.g., Koala bear mother inoculate "pap" with dropping to shift young one from milk to eucalyptus leaves diet) [35]. Fecal microbiome from healthy humans is a mirror of distal gut microbiome which is highly rich in genes involved in the vitamin synthesis, breakdown of nutrients, and metabolism of xenobiotics as compared to already sequenced human genome and microbes genome [4]. The presence of conjugate transposons in gut microbiome is another important source of horizontal gene transfer in bacteria [36]. The HGT is involved not only in spreading antibiotic resistance genes, but also as a source of clinical response of closely related microbial strains of *Salmonella enterica* [37] such as the secretory system type III pathogenicity islands encoded by SPI-I and SPI-II (virulence genes are present in pathogenicity islands, and play a key role in the pathogenesis of *Salmonella* infections through invasion in host cell. Currently, 12 *Salmonella* pathogenicity islands have been investigated with common motifs) [38].

Novel strategies in drug discovery are being pursued by targeting horizontal gene transfer involved in the resistance to antibiotic [39] as well as virulence [40]. Targeting virulence factors with Salmonellosis inhibitors causes less damage to indigenous microbes compared to traditional antibiotic therapy, less selective pressure

for evolution and transfer of resistance and may be more effective against divergent organisms that have acquired a particular virulence factor by HGT. Genomic islands which are a good source of genes and gene transfer systems are also being targeted with small molecule inhibitors that are co-administered with antibiotics to prevent resistance factors by targeted pathogenesis during the therapy [41].

2.5.1 Co-evolution of drug transporters in host and microbes

It has been established that the majority of molecules possessing physiological or pharmacological features are either transported into and or out of the cells by transporting proteins rather than by a passive transport mechanism where drug molecules cross cell membranes through solute transporters that are already involved in the movement of different metabolic intermediary molecules through channels. More than 1000 different types of transporting proteins (transporters) are present in humans [42] comprising solute carriers (SLC) and ATP binding cassettes (ABC) transporters involved in the transport of a broad range of substrates [43].

Human intestinal peptide transporter 1 (hPepT1) belonging to the proton-coupled oligopeptide transporter (POT) family which is also known as solute carrier 15A (SLC15A) is present in the enterocytes, the PepT2 (oligopeptide transporter 2, SLC15A2) in kidney, the PHT1 (peptide histidine transporter 1, SLC15A4) in brain and the PHT2 (peptide histidine transporter 2, SLC15A3) located in spleen, lungs and thymus. Both hPepT1 and PepT2 mediate the transport of di–/tri-peptides and a broad range of peptidomimetics in the organisms, whereas PHT1 and PHT2 mediate the translocation of histidine and with a few selected di- and tri-peptides [44]. The hPepT1, an oligopeptide transporter 1 located in the enterocystes of the small intestine, has low affinity and high capacity transporter protein to transport 400–800 different dipeptides and tripeptides and drugs like ACE'1 (Enalapril) and antiviral (acyclovir) [45]. The hPepT1 is also found in microbes like *Escherichia coli* residing the gut [46, 47] to uptake amino acids and on the microbial outer membrane channels (OmpC and OmpF) present in *E coli* [48] *S. typhi* [49] and *H. influenza* to uptake small and hydrophilic nutrients possessing a molecular weight lower than 600 kDa [50, 51].

Passive diffusion and secondary transport mechanisms in bacteria may involve uptake of drug into bacterial cytoplasm [52, 53]. In the inner membrane of *E. coli,* four protein transporters (PTR) namely YdgR or permease A (DtpA), YjdL, YhiP, and YbgH have been characterized as family members belonging to POT. Among these peptide transporters, the DtpA mediates the transport of dipeptides and tripeptides, thereby exhibiting peptide selectivity very similar to the human oligopeptide transporter (hPepT1) in gut enterocytes [54, 55]. These findings emphasize the potential of modifications of the human physiological state by indirectly modifying the microbiome through drugs [56].

3. Microbiome association with diseases

As described above microorganisms present in the gut of the living organisms contribute to health or cause disease of these organisms by interplay with their immune system. Microbiome is developed at birth according to host interaction but later it is evolved and modified by surrounding factors like environmental and diet. The variation in genetic expression of different individuals is thought to be linked with different microbial composition [57]. Genotype of the host affects the composition of gut microbes. Even mutation of a single gene can cause modification in the structure of gut microbiota. The exact mechanism of association between

the gut microbes and the genotype of host is still unknown. Bifidobacteria are highly prevalent beneficial bacteria in gut microbiome and are associated with lactase non-persistent genotype. This genotype is responsible for the synthesis of lactase enzyme which helps to digest the lactose, present in the milk. Absence of this enzyme leads to lactose intolerance in different organisms. So it is important to investigate susceptibility of different underlying pathological conditions by studying microbiomes association with genotype and environmental factors that vary among different human populations [58].

Different studies showed that metabolic disorders are largely congenital and are associated with different microbiomes. For example, gut microbiomes have been linked to metabolic disorders and obesity [59].

3.1 Gut microbes and gastrointestinal tract (GIT) diseases

In gut microbiome, dysbiosis (imbalance of microbial flora) can be induced by host factors and/or external factors such as the intake of antibiotics, mental and physical stress, and nutrients in the diet. Dysbiosis is likely to impair the regular gut microbiota and the appearance of pathobionts and the production of metabolites which may be dangerous to the host or may deregulate beneficial microbial-derived metabolites. The microbial symbiosis has a significant role in the development of many diseases [60] such as the gastrointestinal diseases [61, 62], infections [63], metabolic disorders, liver diseases [64], autoimmune diseases [65], mental or psychological diseases [66] and respiratory diseases [67].

3.1.1 Inflammatory bowel disease

The inflammatory bowel disease (IBD), which includes Crohn's disease (CD) and ulcerative colitis (UC), has for quite some time been suspected to be a host reaction to its gut microbiota. CD represents the chronic inflammation of the GIT (involving any part from mouth to anus) with idiopathic etiology while UC is the chronic inflammation of the large bowel of the GIT with no known cause. Numerous aspects of the microbiota's association in IBD have been inspected in recent years. About 10–20% of adults and adolescents worldwide are affected by IBD [68]. The precise cause of IBD is unidentified, but it is believed to be a multifactorial disease. Inflammation, infection, visceral hypersensitivity, immunity, genetic factors, motor dysfunction of the GIT as well as psychopathological factors are suspected to play a role in its development [69]. Moreover, abnormal gut microbiota has been noticed in the IBD patients and in animals with intestinal inflammatory disease [70–73]. Some of the metabolically active anaerobic bacteria in the colon and terminal part of ileum interact with the immune system of epithelium and mucosal layer of the host intestine. Continuous stimulation of these microbial antigens promote pathogenic immune responses and may cause defects in the barrier functions of mucous layer by killing some beneficial bacteria or by immune dysregulation, consequently resulting in UC and CD. Moreover, disrupted microbiota structure and function in inflammatory bowel disease intensify the immune response of the host causing dysfunction of epithelium and increased permeability of the mucous layer of the intestine [74].

It is difficult to identify a single factor responsible of IBD; however, several observations have demonstrated a change in the gut microbial composition in IBD patients, both CD and UC [70]. Even though the gut microbiota has been recognized as responsible for the IBD establishment in non-predisposed hosts, numerous researches have revealed a high rate of pathogenic *E. coli* in ileal biopsies of CD patients [74]. *Mycobacterium avium* subspecies *paratuberculosis* is another bacterial

species that has been commonly associated with the CD etiology [75]. Also, in IBD patients, large quantity of *Enterobacteriaceae* and a decline in *Faecalibacterium prausnitzii* was demonstrated to be related to the CD confined to the ileum [76]. However, it is not yet clear whether the IBD-related changes in the gut microbiota are the reason or the result of the disease.

3.1.2 Gastric cancer

For gastric cancer, *H. pylori*-associated chronic inflammation is considered as a risk factor and WHO has classified *H. pylori* as a class I carcinogen. In about 660,000 new cases every year of gastric cancer, *H. pylori* infection is identified as the major cause leading to the acid-producing parietal cells loss, and thereby prompting the gastric atrophy, metaplasia, dysplasia, and finally the formation of carcinoma [77]. The *H. pylori* elimination before the chronic atrophic gastritis may defend against gastric cancer [78]. The cancer-causing risk might be identified with the phylogenetic source of the *H. pylori* strain, host reaction, and host-microorganism communication [79, 80].

3.1.3 Colorectal cancer

Worldwide, the colorectal cancer (CRC) is the fourth most common cause of death associated with cancer [81]. Like other cancers, the CRC is a complex disease related to environmental and genetic factors. Ongoing research has proposed that gut microbiota assumes a role in the convergence of these factors, likely through forming a tumor-advancing environment.

In certain studies, by using a germ-free mice model of adenomatous polyposis coli (APC), a markedly reduced incidence of colonic tumor and a lower tumor load was revealed when compared to normally raised mice. Further other distinct CRC phenotypes such as bleeding from rectum and iron deficiency has also been shown with an invasion of inflammatory cells emerging from an intestinal epithelial barrier dysfunction. Therefore, it seems that the microbiome and host factors (for example, age and genetic predisposition) are important to the CRC growth and progression [82].

3.2 Role of gut microbiota in cardiovascular diseases

Cardiovascular and metabolic disorders are collectively known as cardiometabolic diseases and are associated with high morbidity and mortality along with significant health care expenditures [83]. The gut-derived and endogenously produced endotoxins including indoxyl sulfate, *para*-cresyl sulfate and lipopolysaccharides have been found to be involved in the development of pathological conditions ranging from atherosclerosis to cardio-renal failure or dysfunction [84, 85]. Furthermore, the development of some complex metabolic disorders including insulin resistance and obesity is also associated with differences in the composition of gut microbiota [86]. The metabolites L-carnitine, choline and phosphatidylcholine are metabolized by intestinal microbiota to generate TMA (trimethylamine) which then undergoes oxidation in liver to produce the proatherogenic metabolite known as TMAO (trimethylamine-N-oxide). Moreover, in atherosclerotic plaques was detected bacterial DNA of the intestinal microbiome indicating the direct involvement of intestinal microbiota in the development of atherosclerosis. Therefore, inhibition of intestinal microbiota-mediated TMAO production through dietary modulation has been suggested as a potential approach for treating atherosclerotic cardiovascular diseases [87].

In some earlier research studies, a significantly low synthetic capacity to produce TMA and TMAO from dietary L-carnitine as well as a subsequent lower plasma levels of TMAO have been observed in vegetarians as compared to omnivores. Likewise, significant variations in microbial communities have also been reported in vegetarians as compared to omnivores [88, 89] suggesting that chronic dietary exposure, i.e., omnivores vs. vegetarians, leads to shift of microbial composition with a selective advantage for bacterial species having potential for increased TMA production, and, thus, may interfere with treatment of atherosclerotic cardiovascular diseases.

3.3 Microbiota and integumentary system

The gastrointestinal (GI) system and skin are highly vascularized and densely innervated organs with crucial neuroendocrine and immune roles which are uniquely related to the normal function of skin [90]. Evidence of bidirectional and intimate connection between the gut and skin health as well as a close link between GI health to skin allostasis and homeostasis has been established [91]. GI disturbances resulted often in cutaneous manifestations and the GI system, especially the gut microbiota, appears to participate in the pathophysiology of many inflammatory diseases, i.e., acne, atopic dermatitis and psoriasis [92, 93].

3.3.1 Role of the gut microbiota in skin homeostasis

The mechanism by which GI flora exert their effect on skin homeostasis is still unknown; however it is postulated that probably such effect may be related to the modulatory influence of gut commensals on the systemic immunity [94]. Certain gut microbiota and their metabolites, i.e., polysaccharide A, retinoic acid from *Faecalibacterium prausnitzii*, *Bacteroides fragilis,* and bacteria belonging to the *Clostridium* cluster IV and XI potentiate the accumulation of the lymphocytes and regulatory T cells which assist in the anti-inflammatory responses [90]. In addition to this immunomodulatory effect there is recent evidence that the intestinal microbiota may influence cutaneous pathology, physiology and more directly the modification of the immune response by the metastasis of gut microbiome and their metabolic activity [95].

In cases of disturbance in intestinal barriers, it was found that intestinal bacteria and their metabolites may have the propensity to accumulate in the skin and have also access to the bloodstream which ultimately disrupts skin homeostasis. In fact, DNA of intestinal microbes has been separated from the plasma of psoriatic patients, thus showing a direct connection between the gut microbiota and skin homeostasis [90]. The short chain fatty acids (SCFAs), i.e., acetate, butyrate and propionate resulting from the fermentation of the fibers in GIT are believed to play an important role in the maintenance of certain skin microbiota which consequently affect cutaneous immune defense system. For example, propionic acid has an antimicrobial effect against the most common community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA). Previous literature also demonstrates that SCFAs in skin play an important role in affecting the predominant residence of bacteria on normal human skin. It has been found that *P. acnes* and *S. epidermidis* have higher ability to tolerate the propionic acid than other pathogens. Thus, *P. acnes* and *S. epidermis* fermentation may have a low risk of disrupting the balance of skin microbiome. Altogether, these findings may provide supportive evidence for a functional interactive mechanistic approach between the skin and gut [96].

3.3.2 Dyshomeostasis due to dysbiosis

Intestinal dysbiosis may have the negative potential to affect the skin function since gut microbial flora has a huge potential to produce molecules, both harmful and beneficial, that could then reach the circulation and influence skin. Metabolic products of aromatic amino acids, i.e., *p*-cresol and free-phenols are considered biomarkers of a disturbed gut environment as their production is due to pathogenic bacteria such as *Clostridium difficile*. These metabolites may preferentially accumulate in the skin, enter the circulation blood and disrupt the epidermal differentiation and integrity of the skin barrier [90]. Indeed, high level of *p*-cresol and free-phenols is associated with impaired keratinization and decreased skin hydration [97]. Also, the intestinal dysbiosis is responsible for the increased permeability of epithelium which ultimately modulate the immune response by disrupting their balance with immunosuppressive regulatory T cells and thereby triggers the activation of T cells effectors. It has also been observed that epithelial permeability is further enhanced by the pro-inflammatory cytokines and result in chronic systemic inflammation [98].

3.4 Gut microbiome and pulmonary health

Infectious diseases of the respiratory tract including pneumonia and influenza result in deaths of approximately 3.25 million people annually [99]. The majority of the therapies being used currently are suboptimal because the problems of efficiency, toxicity and antibiotic resistance are difficult to overcome [100]. Most of the respiratory tract infections represent failure of host's immune defense. Recently, it was suggested that gut microbiota plays a crucial role in the initiation and adaptation of the immune response in other distal mucosal sites including lungs. Therefore, it is of interest to understand the underlying mechanisms that regulate the interplay between lung defense and gastrointestinal tract and how this interaction aids in achieving optimal lung health.

3.4.1 Asthma and allergies

An abnormal T-helper type 2 (Th2) cell responses is often associated with asthma and allergies. The Th2 cells are recognized by their ability to synthesize inflammatory cytokines including IL-13, IL-9, IL-5 and IL-4 [101] Evidence suggests that the development of allergic diseases in lung is directly affected by alteration in gut immune response [65]. In fact, a single oral dose of *Candida albicans* administered to antibiotic treated mice resulted in dysbiosis, i.e., an altered composition of the gut microbiome. These treated mice exhibited more CD4 cell mediated inflammation response in lung after aerosol administration of an allergen in comparison to those mice having normal intestinal flora [102], suggesting that an immunological predisposition to respiratory allergies can be facilitated by an altered gut microbiome. There is also an increasing interest in understanding the role of Th9 and Th17 cells in the development of asthma and allergies.

3.4.2 Viral and bacterial respiratory infections

Gut microbiota also plays a critical role in the immune response to respiratory tract viral infections like influenza. In infected mice, the CD8 and CD4 T cell subpopulations are directly influenced by the intestinal microbiota [103]. It has also been suggested that an intact intestinal microbiota is necessary for the expression of

pro-inflammatory cytokines including pro-IL-18 and pro-IL-1β, which are essential for clearance of influenza [104]. This indicates that microbial signals are provided by gut microbiota which are crucial for the shaping and priming the immune response to viral pneumonia.

Similar findings regarding the role of gut microbiome in immune response to respiratory bacterial infections have also been observed in germ-free mice. These mice were found to be more susceptible to pulmonary infection caused by bacterial pathogen *Klebsiella pneumonia*, showing increased levels of IL-10 and suppressed recruitment of neutrophil that allows dissemination and growth of pathogens [105].

3.5 Gut microbiome and pregnancy

All systems of the body including maternal microbiome are affected by pregnancy. Changes in gut and vaginal microbiome during gestation are of particular significance because during vaginal delivery there is vertical transmission of microbes to the newborn [106–108]. During pregnancy the vaginal microbiota composition changes throughout the gestation period. In addition to vaginal microbiome, the maternal intestinal microbiome also undergoes change during pregnancy. It has been reported that bacterial diversity decreases in women as the pregnancy progresses [107]. Particularly, the ratio of pro-inflammatory *Proteobacteria,* which includes the *Streptococcus* genus and *Enterobacteriaceae* family, reduces during first and third trimester, while an increase in the anti-inflammatory *Faecalibacterium prausnitzii* occurs during these trimesters of pregnancy. These changes in microbiome are independent of body weight during pregnancy, diet, antibiotic use and gestational diabetes, suggesting the association of these changes with normal physiological pregnancy-related alteration in maternal immune and endocrine systems [109].

The consequences of changes in maternal vaginal and gut microbiota on mother health are not clear; however, the gestational changes in fecal and vaginal microbiota are considered to be important for the adaptive response necessary for protection as well as to promote the fetus health. These changes also help in providing a particular microbial inoculum to the newborn at birth before its exposure to other environmental microbes. Also the microbial communities' composition in maternal vagina and gut are not independent of each other. In fact, in pregnant women of 35–37 weeks of gestation most of bacteria, including species of *Bifidobacterium* and *Lactobacillus*, are common between vagina and rectum [110].

Some research studies reported that shift in gut microbiota of mother during pregnancy may be an adaptive response for the mother and newborn health. In mice, an increase in the gut bacteria associated with gestational age, promotes body weight gain indicating a co-evolution of these microbes with their hosts during pregnancy [107]. Moreover, during vaginal delivery, the vertical transmission of these maternal gut microbiomes to the neonate may help the newborn to get an immediate access to microbiota at birth [107, 111].

4. Role of gut-microbiome in brain physiology

Both extrinsic and intrinsic factors play an important role to regulate the development and maturation of the central nervous system (CNS) in humans. In germ-free and antibiotic-treated animals the physiology of the CNS can be affected by neurochemistry as well as by specific microbiota [112]. Evidences for interaction between neuropsychiatric and gastrointestinal pathology in humans have been reported in different psychiatric conditions including autism, depression and anxiety [113].

The role of gut-brain interaction in the nervous system development is also recognized. Gut-brain axis actually establishes a relationship between gut-microbiota and their interaction with brain leading to changes in the status of the CNS. The dysbiosis in microbial species of the gut may lead to induce imbalance in host homeostasis, atypical immune signaling and ultimately progression of CNS diseases [114].

The permeable blood brain barrier (BBB) and functional lymphatic vessels residing in dura meningeal membrane may serve as a gateway for transmission of signals [115]. The exposure to several environmental factors can affect the generation of neurons during the development of the CNS [113]. It has been suggested that maternal-fetal interface permeability permits regulatory factors from the gut microbiota to stimulate Toll-like receptor 2 (TLR2) that helps to promote neural development of fetus and also impart its effects on cognitive function during adulthood [116].

The combination of microbial strains (especially the probiotic) can actively counteract the deficient neurogenesis which further strengthen the developmental link of microbiome to the hippocampal neuronal generation [117]. The brain-blood barrier (BBB) is a highly selective and semipermeable barricade that permits the passage of neutral, low molecular weight and lipidic soluble molecules [118]. In the development of the structural components and growth of vasculature, BBB requires arachidonic acid (AA) and decohexaenoic acid (DHA) which are provided as polyunsaturated fatty acids (PUFA) by gut microbiome [119]. It has been demonstrated that the restoration of BBB is possible in germ-free mice by colonization of *Clostridium tyrobutyricum* that produce high level of butyrates [120].

5. Impact of different environmental conditions on gut microbiome

The most important environmental factors that may lead to dysbiosis include (i) Physical or psychological stress, (ii) use of antibiotics, and (iii) diet (**Figure 2**).

5.1 Physical or psychological stress

Stress is usually defined as homeostasis disruption due to physical, psychological or environmental stimuli known as stressors leading to adaptive behavioral and physiological response in order to restore homeostasis [121]. The effect of both psychological and physical stress on gut microbiome is widely recognized and has been observed in both humans as well as animals [122]. Some research conducted in mice has shown that the microbial composition in the cecum was altered in response to the exposure of a social stressor by placing an aggressive male mouse into the cages of non-aggressive mice. Furthermore, the plasma concentration of stress hormones such as adrenocorticotropic hormone (ACTH) and corticosterone was found to be significantly higher in germ-free mice as compared to specific pathogen-free mice. In addition, several stressors including acoustic stress, self-control conditions and food deprivation have a negative impact on the gut microbiome resulting in the impairment of the immune system [123, 124].

5.2 Use of antibiotics

It has been observed in both humans and animals that the treatment with antibiotics can result in a decreased population of beneficial bacteria including *Lactobacilli* and *Bifidobacteria* along with the increased population of potential pathogenic bacteria like *Clostridium difficile* and the pathogenic yeast *Candida albicans*. The GI symptoms for example diarrhea, abdominal pain, bloating as well as yeast infections may occur in response to microbial shifts or dysbiosis. However,

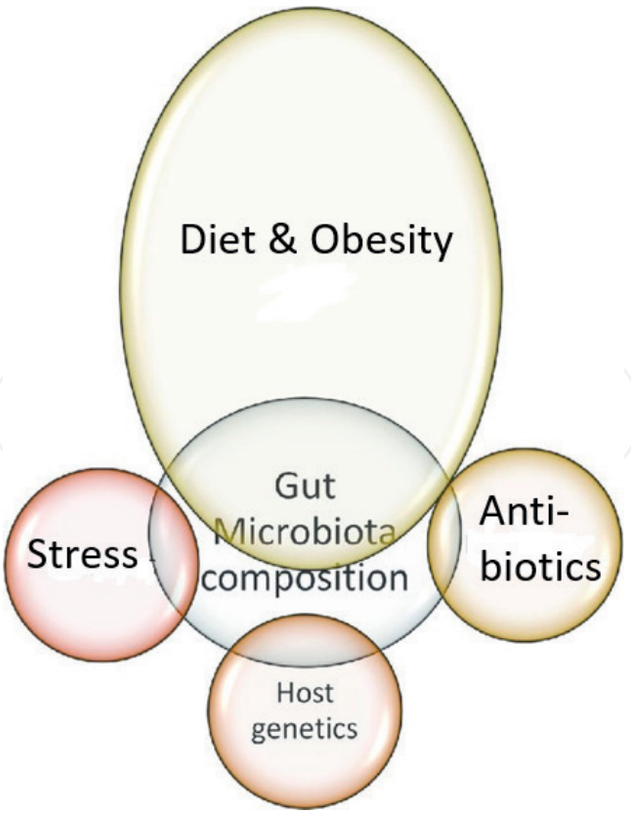

Figure 2.
Environmental factors influencing gut microbiota.

more serious and long-lasting consequences have been suggested. For example, it was reported that at the end of a 5-day treatment with the antibiotic ciprofloxacin, most of the gut bacteria was restored to the pre-treatment levels in 4 weeks, but some intestinal bacteria failed to recover even after 6-months. Moreover, a 7-day treatment with clindamycin, a drug of choice for treatment of *Bacteroides* infections, resulted in disrupted gut microbiome for up to 2 years [125].

5.3 Diet and obesity

Food is metabolized by the gut microbial species to extract nutrients, but some microbial species are more efficient in extracting nutrients from food as compared to other species. As different individuals have slightly different microbial populations, it is probable that more nutrients are harvested by some people's gut microbes making them perhaps more prone to become overweight. A high percentage of *Firmicutes* was found in the gut microbiome of genetically obese mice while a high percentage of *Bacteriodetes* were observed in lean mice. Similar observation was reported in lean and obese human volunteers. Moreover, it was also seen that the obese people who used a low-caloric diet to lose weight, their gut microbiota shifted to a similar bacterial population as observed in lean people [125].

6. Conclusions

The human body is a super-organism consisting of 10 times more microbial cells than our own body cells. The body's assortment of microorganisms is mainly in gastrointestinal tract, collectively called the gut microbiota. It can be comparable to an organ in because it performs functions necessary for our survival by contributing directly and/or indirectly in various physiological processes. For the

past decade, human gut microbiota has been extensively studied as many scientists believe that human health mainly depends on microbes that are living on or in our body apart from our own genome. Recently, research findings have suggested that gut microbiome is evolving as a new organ system mainly due to its specific biochemical interaction with its host which affirm its systemic integration into the host physiology as gut bacteria are not only critical for regulating gut metabolism, but also important for other systems of host including immune system. The focus of this chapter was to highlight the importance of gut microorganisms as a new organ system and their possible involvement with host systems as well as the metabolism of different drugs and nutrients in the gut by these microbes. So, in this chapter, we have reviewed opinions of different researchers about the role of gut microbiota in maintaining health as well as its contributory role in different ailments. However, literature revealed that the involvement of gut microbiota in altering host genetics effecting disease progression needs further investigations.

Author details

Haseeb Anwar[1*], Shahzad Irfan[1], Ghulam Hussain[1], Muhammad Naeem Faisal[2], Humaira Muzaffar[1], Imtiaz Mustafa[1], Imran Mukhtar[1], Saima Malik[1] and Muhammad Irfan Ullah[3]

1 Department of Physiology, Government College University, Faisalabad, Pakistan

2 Institute of Pharmacy, Physiology and Pharmacology, University of Agriculture, Faisalabad, Pakistan

3 Department of Pathobiology, Faculty of Veterinary Sciences, Bahauddin Zakariya University, Multan, Pakistan

*Address all correspondence to: drhaseebanwar@gcuf.edu.pk

References

[1] Van den Abbeele P et al. The host selects mucosal and luminal associations of coevolved gut microorganisms: A novel concept. FEMS Microbiology Reviews. 2011;**35**(4):681-704

[2] Pickard JM et al. Gut microbiota: Role in pathogen colonization, immune responses, and inflammatory disease. Immunological Reviews. 2017;**279**(1):70-89

[3] Faust K et al. Microbial co-occurrence relationships in the human microbiome. PLoS Computational Biology. 2012;**8**(7):e1002606

[4] Gill SR et al. Metagenomic analysis of the human distal gut microbiome. Science. 2006;**312**(5778):1355-1359

[5] Ley RE et al. Microbial ecology: Human gut microbes associated with obesity. Nature. 2006;**444**(7122):1022

[6] Chen Z et al. Incorporation of therapeutically modified bacteria into gut microbiota inhibits obesity. The Journal of Clinical Investigation. 2014;**124**(8):3391-3406

[7] Martin FPJ et al. A top-down systems biology view of microbiome-mammalian metabolic interactions in a mouse model. Molecular Systems Biology. 2007;**3**(1):112

[8] Dethlefsen L, McFall-Ngai M, Relman DA. An ecological and evolutionary perspective on human–microbe mutualism and disease. Nature. 2007;**449**(7164):811

[9] Sison-Mangus MP, Mushegian AA, Ebert D. Water fleas require microbiota for survival, growth and reproduction. The ISME Journal. 2015;**9**(1):59

[10] Sampson TR, Mazmanian SK. Control of brain development, function, and behavior by the microbiome. Cell Host & Microbe. 2015;**17**(5):565-576

[11] McKenney PT, Pamer EG. From hype to hope: The gut microbiota in enteric infectious disease. Cell. 2015;**163**(6):1326-1332

[12] Nicholson JK et al. Host-gut microbiota metabolic interactions. Science. 2012;**336**(6086):1262-1267

[13] Zilber-Rosenberg I, Rosenberg E. Role of microorganisms in the evolution of animals and plants: The hologenome theory of evolution. FEMS Microbiology Reviews. 2008;**32**(5):723-735

[14] Rosenberg E, Zilber-Rosenberg I. The Hologenome Concept: Human, Animal and Plant Microbiota. Switzerland: Springer; 2014

[15] Blaser MJ, Cardon ZG, Cho MK, Dangl JL, Donohue TJ, Green JL et al. Toward a predictive understanding of Earth's microbiomes to address 21st century challenges. mBio. 2016;**7**(3):e00714-16.

[16] Izard J, Rivera M. Metagenomics for Microbiology. Academic Press Elsevier Science; 2014

[17] Macia L et al. Microbial influences on epithelial integrity and immune function as a basis for inflammatory diseases. Immunological Reviews. 2012;**245**(1):164-176

[18] Falony G et al. Population-level analysis of gut microbiome variation. Science. 2016;**352**(6285):560-564

[19] Heinken A, Thiele I. Systematic prediction of health-relevant human-microbial co-metabolism through a computational framework. Gut Microbes. 2015;**6**(2):120-130

[20] Ley RE, Peterson DA, Gordon JI. Ecological and evolutionary forces

shaping microbial diversity in the human intestine. Cell. 2006;**124**(4):837-848

[21] Sansonetti PJ, Medzhitov R. Learning tolerance while fighting ignorance. Cell. 2009;**138**(3):416-420

[22] Yang L et al. Gut microbiota co-microevolution with selection for host humoral immunity. Frontiers in Microbiology. 2017;**8**:1243

[23] Tissier H. Recherches sur la flore intestinale des nourrissons: (état normal et pathologique). G. Carre and C. Naud, Paris, France; 1900

[24] Blaser MJ. Who are we? Indigenous microbes and the ecology of human diseases. EMBO Reports. 2006;**7**(10):956-960

[25] Ardissone AN et al. Meconium microbiome analysis identifies bacteria correlated with premature birth. PLoS One. 2014;**9**(3):e90784

[26] Moles L et al. Bacterial diversity in meconium of preterm neonates and evolution of their fecal microbiota during the first month of life. PLoS One. 2013;**8**(6):e66986

[27] DiGiulio DB et al. Microbial prevalence, diversity and abundance in amniotic fluid during preterm labor: A molecular and culture-based investigation. PLoS One. 2008;**3**(8):e3056

[28] Moeller AH et al. Transmission modes of the mammalian gut microbiota. Science. 2018;**362**(6413):453-457

[29] Rothschild D et al. Environment dominates over host genetics in shaping human gut microbiota. Nature. 2018;**555**(7695):210

[30] Madupu R, Szpakowski S, Nelson KE. Microbiome in human health and disease. Science Progress. 2013;**96**(2):153-170

[31] Zaneveld J et al. Host-bacterial coevolution and the search for new drug targets. Current Opinion in Chemical Biology. 2008;**12**(1):109-114

[32] Moran NA. Symbiosis as an adaptive process and source of phenotypic complexity. Proceedings of the National Academy of Sciences. 2007;**104** (Suppl. 1):8627-8633

[33] Charleston MA, Perkins SL. Traversing the tangle: Algorithms and applications for cophylogenetic studies. Journal of Biomedical Informatics. 2006;**39**(1):62-71

[34] Stevens J. Computational aspects of host–parasite phylogenies. Briefings in Bioinformatics. 2004;**5**(4):339-349

[35] Osawa R, Blanshard W, Ocallaghan P. Microbiological studies of the intestinal microflora of the koala, *Phascolarctos cinereus*. 2. Pap, a special maternal feces consumed by juvenile koalas. Australian Journal of Zoology. 1993;**41**(6):611-620

[36] Kurokawa K et al. Comparative metagenomics revealed commonly enriched gene sets in human gut microbiomes. DNA Research. 2007;**14**(4):169-181

[37] Hansen-Wester I, Stecher B, Hensel M. Analyses of the evolutionary distribution of *Salmonella* translocated effectors. Infection and Immunity. 2002;**70**(3):1619-1622

[38] Hensel M. Evolution of pathogenicity islands of *Salmonella enterica*. International Journal of Medical Microbiology. 2004;**294**(2-3):95-102

[39] Lujan SA et al. Disrupting antibiotic resistance propagation by inhibiting the conjugative DNA relaxase. Proceedings

of the National Academy of Sciences. 2007;**104**(30):12282-12287

[40] Dahlgren MK et al. Design, synthesis, and multivariate quantitative structure– activity relationship of Salicylanilides potent inhibitors of type III secretion in Yersinia. Journal of Medicinal Chemistry. 2007;**50**(24):6177-6188

[41] Hsiao WW et al. Evidence of a large novel gene pool associated with prokaryotic genomic islands. PLoS Genetics. 2005;**1**(5):e62

[42] Ekins S et al. Computational modeling to accelerate the identification of substrates and inhibitors for transporters that affect drug disposition. Clinical Pharmacology & Therapeutics. 2012;**92**(5):661-665

[43] Dobson PD, Kell DB. Carrier-mediated cellular uptake of pharmaceutical drugs: An exception or the rule? Nature Reviews Drug Discovery. 2008;**7**(3):205

[44] Rubio-Aliaga I, Daniel H. Peptide transporters and their roles in physiological processes and drug disposition. Xenobiotica. 2008;**38**(7-8):1022-1042

[45] Ma K, Hu Y, Smith DE. Peptide transporter 1 is responsible for intestinal uptake of the dipeptide glycylsarcosine: Studies in everted jejunal rings from wild-type and Pept1 null mice. Journal of Pharmaceutical Sciences. 2011;**100**(2):767-774

[46] Sussman A, Gilvarg C. Peptide transport and metabolism in bacteria. Annual Review of Biochemistry. 1971;**40**(1):397-408

[47] payne JW. Peptide Transport in Bacteria: Methods, Mutants and Energy Coupling. Biochemical Society Transactions. Portland Press Limited. 1983;**11**:794-798

[48] Mortimer PG, Piddok LJ. The accumulation of five antibacterial agents in porin-deficient mutants of Escherichia coli. Journal of Antimicrobial Chemotherapy. 1993;**32**(2):195-213

[49] Toro CS et al. Clinical isolate of a porinless *Salmonella typhi* resistant to high levels of chloramphenicol. Antimicrobial Agents and Chemotherapy. 1990;**34**(9):1715-1719

[50] Burns JL, Smith AL. A major outer-membrane protein functions as a porin in *Haemophilus influenzae*. Microbiology. 1987;**133**(5):1273-1277

[51] Srikumar R et al. Porins of *Haemophilus influenzae* type b mutated in loop 3 and in loop 4. Journal of Biological Chemistry. 1997;**272**(21):13614-13621

[52] Lewinson O et al. The *Escherichia coli* multidrug transporter MdfA catalyzes both electrogenic and electroneutral transport reactions. Proceedings of the National Academy of Sciences. 2003;**100**(4):1667-1672

[53] Abdel-Sayed S. Transport of chloramphenicol into sensitive strains of *Escherichia coli* and *Pseudomonas aeruginosa*. Journal of Antimicrobial Chemotherapy. 1987;**19**(1):7-20

[54] Harder D et al. DtpB (YhiP) and DtpA (TppB, YdgR) are prototypical proton-dependent peptide transporters of *Escherichia coli*. The FEBS Journal. 2008;**275**(13):3290-3298

[55] Casagrande F et al. Projection structure of DtpD (YbgH), a prokaryotic member of the peptide transporter family. Journal of Molecular Biology. 2009;**394**(4):708-717

[56] Garber K. Drugging the Gut Microbiome. Nature Publishing Group; 2015;**33**:228-231

[57] Pessione E. Lactic acid bacteria contribution to gut microbiota complexity: Lights and shadows. Frontiers in Cellular and Infection Microbiology. 2012;**2**:86

[58] Goodrich JK et al. The relationship between the human genome and microbiome comes into view. Annual Review of Genetics. 2017;**51**:413-433

[59] Snyder M. Genomics and Personalized Medicine: What Everyone Needs to Know. England: Oxford University Press; 2016

[60] Bassi C, Larvin M, Villatoro E. Antibiotic therapy for prophylaxis against infection of pancreatic necrosis in acute pancreatitis. The Cochrane Database of Systematic Reviews. 2003;**4**:CD002941

[61] Bik EM et al. Bacterial diversity in the oral cavity of 10 healthy individuals. The ISME Journal. 2010;**4**(8):962

[62] Bik EM et al. Molecular analysis of the bacterial microbiota in the human stomach. Proceedings of the National Academy of Sciences. 2006;**103**(3):732-737

[63] Bates JM et al. Intestinal alkaline phosphatase detoxifies lipopolysaccharide and prevents inflammation in zebrafish in response to the gut microbiota. Cell Host & Microbe. 2007;**2**(6):371-382

[64] Beutler B, Rietschel ET. Innate immune sensing and its roots: The story of endotoxin. Nature Reviews Immunology. 2003;**3**(2):169

[65] Björkstén B et al. Allergy development and the intestinal microflora during the first year of life. Journal of Allergy and Clinical Immunology. 2001;**108**(4):516-520

[66] Björkbacka H et al. Reduced atherosclerosis in MyD88-null mice links elevated serum cholesterol levels to activation of innate immunity signaling pathways. Nature Medicine. 2004;**10**(4):416

[67] Bingham S. Diet and Colorectal Cancer Prevention. Portland Press Limited; 2000

[68] Longstreth GF et al. Functional bowel disorders. Gastroenterology. 2006;**130**(5):1480-1491

[69] Ghoshal UC et al. The gut microbiota and irritable bowel syndrome: Friend or foe? International Journal of Inflammation. 2012:**151085**

[70] Peterson DA et al. Metagenomic approaches for defining the pathogenesis of inflammatory bowel diseases. Cell Host & Microbe. 2008;**3**(6):417-427

[71] Frank DN, Pace NR. Gastrointestinal microbiology enters the metagenomics era. Current Opinion in Gastroenterology. 2008;**24**(1):4-10

[72] Frank DN et al. Molecular-phylogenetic characterization of microbial community imbalances in human inflammatory bowel diseases. Proceedings of the National Academy of Sciences. 2007;**104**(34):13780-13785

[73] Lupp C et al. Host-mediated inflammation disrupts the intestinal microbiota and promotes the overgrowth of *Enterobacteriaceae*. Cell Host & Microbe. 2007;**2**(2):119-129

[74] Sartor RB. Microbial influences in inflammatory bowel diseases. Gastroenterology. 2008;**134**(2):577-594

[75] Packey CD, Sartor RB. Commensal bacteria, traditional and opportunistic pathogens, dysbiosis and bacterial killing in inflammatory bowel diseases. Current Opinion in Infectious Diseases. 2009;**22**(3):292

[76] Willing B et al. Twin studies reveal specific imbalances in the mucosaassociated microbiota of patients with ileal Crohn's disease. Inflammatory Bowel Diseases. 2008;**15**(5):653-660

[77] De Martel C et al. Global burden of cancers attributable to infections in 2008: A review and synthetic analysis. The Lancet Oncology. 2012;**13**(6):607-615

[78] Wong BC-Y et al. *Helicobacter pylori* eradication to prevent gastric cancer in a high-risk region of China: A randomized controlled trial. JAMA. 2004;**291**(2):187-194

[79] El-Omar EM et al. Interleukin-1 polymorphisms associated with increased risk of gastric cancer. Nature. 2000;**404**(6776):398

[80] de Sablet T et al. Phylogeographic origin of *Helicobacter pylori* is a determinant of gastric cancer risk. Gut. 2011;**60**(9):1189-1195

[81] Arnold M et al. Global patterns and trends in colorectal cancer incidence and mortality. Gut. 2017;**66**(4):683-691

[82] Li Y et al. Gut microbiota accelerate tumor growth via c-jun and STAT3 phosphorylation in APC Min/+ mice. Carcinogenesis. 2012;**33**(6):1231-1238

[83] Aron-Wisnewsky J, Clément K. The gut microbiome, diet, and links to cardiometabolic and chronic disorders. Nature Reviews Nephrology. 2016;**12**(3):169

[84] Buffie CG, Pamer EG. Microbiota-mediated colonization resistance against intestinal pathogens. Nature Reviews Immunology. 2013;**13**(11):790

[85] Collins SM. A role for the gut microbiota in IBS. Nature Reviews Gastroenterology & Hepatology. 2014;**11**(8):497

[86] Turnbaugh PJ et al. An obesity-associated gut microbiome with increased capacity for energy harvest. Nature. 2006;**444**(7122):1027

[87] Wang Z et al. Non-lethal inhibition of gut microbial trimethylamine production for the treatment of atherosclerosis. Cell. 2015;**163**(7):1585-1595

[88] Koeth RA et al. Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis. Nature Medicine. 2013;**19**(5):576

[89] Huijbers MM et al. Flavin dependent monooxygenases. Archives of Biochemistry and Biophysics. 2014;**544**:2-17

[90] O'Neill CA et al. The gut-skin axis in health and disease: A paradigm with therapeutic implications. BioEssays. 2016;**38**(11):1167-1176

[91] Levkovich T et al. Probiotic bacteria induce a 'glow of health'. PLoS One. 2013;**8**(1):e53867

[92] Shah KR et al. Cutaneous manifestations of gastrointestinal disease: Part I. Journal of the American Academy of Dermatology. 2013;**68**(2):189. e1-189. e21

[93] Salem I et al. The gut microbiome as a major regulator of the gut-skin axis. Frontiers in Microbiology. 2018;**9**:1459

[94] Forbes JD, Van Domselaar G, Bernstein CN. The gut microbiota in immune-mediated inflammatory diseases. Frontiers in Microbiology. 2016;**7**:1081

[95] Samuelson DR, Welsh DA, Shellito JE. Regulation of lung immunity and host defense by the intestinal microbiota. Frontiers in Microbiology. 2015;**6**:1085

[96] Schwarz A, Bruhs A, Schwarz T. The short-chain fatty acid sodium butyrate functions as a regulator of the skin immune system. Journal of Investigative Dermatology. 2017;**137**(4): 855-864

[97] Miyazaki K et al. Bifidobacterium fermented milk and galacto-oligosaccharides lead to improved skin health by decreasing phenols production by gut microbiota. Beneficial Microbes. 2013;**5**(2):121-128

[98] Kosiewicz MM et al. Relationship between gut microbiota and development of T cell associated disease. FEBS Letters. 2014;**588**(22):4195-4206

[99] Ruberto I et al. The availability and consistency of dengue surveillance data provided online by the World Health Organization. PLoS Neglected Tropical Diseases. 2015;**9**(4):e0003511

[100] Keely S, Talley NJ, Hansbro PM. Pulmonary-intestinal cross-talk in mucosal inflammatory disease. Mucosal Immunology. 2012;**5**(1):7

[101] McLoughlin RM, Mills KH. Influence of gastrointestinal commensal bacteria on the immune responses that mediate allergy and asthma. Journal of Allergy and Clinical Immunology. 2011;**127**(5):1097-1107

[102] Noverr MC et al. Role of antibiotics and fungal microbiota in driving pulmonary allergic responses. Infection and Immunity. 2004;**72**(9):4996-5003

[103] Ichinohe T et al. Microbiota regulates immune defense against respiratory tract influenza a virus infection. Proceedings of the National Academy of Sciences. 2011;**108**(13):5354-5359

[104] Ichinohe T, Pang IK, Iwasaki A. Influenza virus activates inflammasomes via its intracellular M2 ion channel. Nature Immunology. 2010;**11**(5):404

[105] Fagundes CT et al. Transient TLR activation restores inflammatory response and ability to control pulmonary bacterial infection in germfree mice. The Journal of Immunology. 2012;**188**(3):1411-1420

[106] Aagaard K et al. A metagenomic approach to characterization of the vaginal microbiome signature in pregnancy. PLoS One. 2012;**7**(6):e36466

[107] Koren O et al. Host remodeling of the gut microbiome and metabolic changes during pregnancy. Cell. 2012;**150**(3):470-480

[108] Romero R et al. The composition and stability of the vaginal microbiota of normal pregnant women is different from that of non-pregnant women. Microbiome. 2014;**2**(1):4

[109] Mueller NT et al. The infant microbiome development: Mom matters. Trends in Molecular Medicine. 2015;**21**(2):109-117

[110] El Aila NA et al. Identification and genotyping of bacteria from paired vaginal and rectal samples from pregnant women indicates similarity between vaginal and rectal microflora. BMC Infectious Diseases. 2009;**9**(1):167

[111] Pantoja-Feliciano IG et al. Biphasic assembly of the murine intestinal microbiota during early development. The ISME Journal. 2013;**7**(6):1112

[112] Smith PA. The tantalizing links between gut microbes and the brain. Nature News. 2015;**526**(7573):312

[113] Sharon G et al. The central nervous system and the gut microbiome. Cell. 2016;**167**(4):915-932

[114] Cussotto S et al. The neuroendocrinology of the

microbiota-gut-brain axis: A behavioural perspective. Frontiers in Neuroendocrinology. 2018;**51**:80-101

[115] Quail DF, Joyce JA. The microenvironmental landscape of brain tumors. Cancer Cell. 2017;**31**(3):326-341

[116] Humann J et al. Bacterial peptidoglycan traverses the placenta to induce fetal neuroproliferation and aberrant postnatal behavior. Cell Host & Microbe. 2016;**19**(3):388-399

[117] Möhle L et al. Ly6Chi monocytes provide a link between antibiotic-induced changes in gut microbiota and adult hippocampal neurogenesis. Cell Reports. 2016;**15**(9):1945-1956

[118] Wolak DJ, Thorne RG. Diffusion of macromolecules in the brain: Implications for drug delivery. Molecular Pharmaceutics. 2013;**10**(5):1492-1504

[119] Crawford M et al. The potential role for arachidonic and docosahexaenoic acids in protection against some central nervous system injuries in preterm infants. Lipids. 2003;**38**(4):303-315

[120] Braniste V et al. The gut microbiota influences blood-brain barrier permeability in mice. Science Translational Medicine. 2014;**6**(263):263ra158

[121] Glaser R, Kiecolt-Glaser JK. Stress-induced immune dysfunction: Implications for health. Nature Reviews Immunology. 2005;**5**(3):243

[122] Caso JR, Leza JC, Menchen L. The effects of physical and psychological stress on the gastrointestinal tract: Lessons from animal models. Current Molecular Medicine. 2008;**8**(4):299-312

[123] Bailey MT et al. Exposure to a social stressor alters the structure of the intestinal microbiota: Implications for stressor-induced immunomodulation. Brain, Behavior, and Immunity. 2011;**25**(3):397-407

[124] Sudo N et al. Postnatal microbial colonization programs the hypothalamic–pituitary–adrenal system for stress response in mice. The Journal of Physiology. 2004;**558**(1):263-275

[125] Phillips ML. Gut reaction: Environmental effects on the human microbiota. National Institute of Environmental Health Sciences. 2009;**117**(5):A198–A205