Impact of Human Microbiome on Health

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Abstract

The human genome in the recent years, by the advent of technological advancements, has emerged as a major prolocutor for reciprocity between the human body and the food consumed. As known, microbiome comprises all the genetic materials within a microbiota and can thereby be also referred to as metagenome of the microbiota. Contemporary researches have revealed the influence of microbiome not only on human mind and health status, but also in wide range of disease switching, ranging from cardio-metabolic diseases, allergies and obesities to life-threatening diseases such as cancer. Though the complete mechanism of many diseases is yet unclear, research works have revealed that the metabolites, nutrients and microbes can be regarded as the key players for such physiological state. The major approach of this chapter is to enlighten the interrelationship of the microbiome on the human health either in a synergistic or in an antagonistic manner.

Keywords

Genome · Microbiome · Microbiota

20.1 Introduction

In the last few decades, immense initiatives have been taken in understanding the role of microbiome on human health. In the present day, either in the field of therapeutic development or medical treatment, the impact of microbiome is

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especially apparent in the studies of different microbial communities and the human microbiome. In the recent times, 'omics' has provided a significant impetus on all the facets of biological research which has ushered the field to gain in momentum. The study, which is contemporarily popularised as study of 'human microbiome', is an outcome of the advancement in the field of genomics and other fields of microbiology, which has given the classical microbiology a new outlook and perspective. Thereby, the attention was driven and directed towards the genomics, which was the major objective of the Human Microbiome Project (HMP) (Turnbough and Wilson 2007). The HMP was used for the characterisation of all the microbial communities living in the human body, eventually switching the interest towards, not only, the type of microbes existing in the human body but also to the role and activity they perform both in the case of a healthy and diseased individual. Since 2003, after the publication of the first human genome (Chial 2008), the biomedical research on microbiome has obtained a significant scientific attention. There has been an immense leap from the culture-based surveys of various tissues or organs, for example, of gut and oral cavity, to molecular profiling of the microbial communities and their biochemical products like enzymes, proteins, and amino acids in all the different ecological niches of the human body (Eckburg et al. 2005; Gill et al. 2006; Costello et al. 2009) for this subject. This chapter attempts to put an insight into the distribution and diversification of human microbiome, the behaviour of human microbiome on the human health and microbiome as a paradigm for the future nutritional and medicinal strategies for human benefits.

20.2 Systemic Microbiome: Its Distribution and Diversification

Over 100 trillion microbes are estimated to be residing both inside and over the surface of humans, possessing genome which is approximately 150 times to that of the entire human being (Wang et al. 2017). This includes microbes of different families such as bacteria, fungi, archaea and viruses, contributing about eight million unique protein-coding genes as compared to the human genome, which comprises only around 22,000 protein-coding genes (Tomayko et al. 2013). This variation and the nature of the organism, specific to the specific anatomic site of the body, is a consequence of their specific growth requirement. The other determinants for such growth include coevolution of microorganism, their extensive interaction amongst each other and with the human host, variation in the composition and function with respect to the population, human life span and inconsistency of the body sites, ecologic condition, difference in the oxygen tension, airway luminal temperature, mechanism of muco-ciliary clearance, sex, genetics and socio-economic status. Hence, there has been a development of the concept of interdependence, in variety of physiologic, immunologic and metabolic processes, which ultimately determines the microbiome community in a particular site of the human body system.

20.2.1 The Gut Microbiome

Amongst all the human systemic microbiome, the gut microbiome, composed of the genetic material of the microorganisms in the gut, occupies a very essential and special position. They play an important role in various physiological processes like metabolism, immunity development and nourishment supply. The genotype and the immune system of the host have been shown to contribute towards the development of gut microbiota (Thaiss et al. 2016). In response to environmental factors, such as diet, pathogens and xenobiotic substances, a crosstalk occurs between the human immune system and the microbiome. For instance, the myeloid cells, epithelial layer and the innate lymphoid cells, part of the immune system, crosstalks with the gut microbiota for which the microbiome composition, host physiology and disease susceptibility are the main consequences of such crosstalks and feedback loops between them. Along with the bacterial community, like Firmicutes and Bacteroidetes species (Table 20.1), these interactions are also contributed by the other microbiota like fungi (Pothoulakis 2009), archaea and viruses (Breitbart et al. 2003). Though the understanding of the immunological relationship between the fungi and archaea is limited currently, the trans-kingdom commensalism is expected to be formed from infancy (LaTuga et al. 2011).

The principal constituents are the bacteriome, virome and mycobiome, whose strong interdependence maintains the functionality of the gut microbiota, if imbalanced may also affect the other systems in various ways. Since the time of birth of an individual, when the sterile gut of the neonate gets exposed to the biota of mother's vagina during the vaginal delivery or hospital microbiota in case of caesarean section (which may even include the multidrug-resistant species), the microbes starts their colonisation with an eventual change by the age of 3–5 years, by when an individual starts resembling bacterial community to that of an adult both structurally and functionally (Bull and Plummer 2014). In adults, the composition of gut microbiota is uneven throughout the length of the gut. As compared to small intestine, which is rich in the species related to phylum *Firmicutes*, colon on the contrary exhibits the presence of members of phylum Bacteroidetes. The microbiome of lumen and that attached to the epithelial lining even show differences. The stool sample exhibited the presence of *Bacteroides, Streptococcus, Ruminococcus, Lactobacillus, Enterococcus, Bifidobacterium* and *Clostridium* which presented the lumen community while on the mucous layer detected the presence of *Enterococcus, Lactobacillus* and *Clostridium* (Swidsinski et al. 2005).

20.2.2 The Microbiome of the Lungs and the Airways

During the initiation of HMP, the airways and lungs were exempted from the study, believing these parts to be sterile in nature (Moffatt and Cookson 2017). This fact was always acceptable because of the negative results yielded by the various standard microbiological culture tests of the healthy individuals (Faner et al. 2017). Its study was also a challenge owing to the difficulty in assessing the lower

Table 20.1 Distribution and diversity of human microbiome

Site	Name of dominant species	Average genome size	References
Oral	*Streptococcus, Haemophilus, Actinomyces, Prevotella*	2.11 Mb	Nayfach and Pollard (2015) and Gao et al. (2018)
Gut	*Firmicutes, Bacteroidetes, Bacteroides, Streptococcus, Ruminococcus, Enterococcus, Bifidobacterium, Clostridium, Enterococcus, Lactobacillus* and *Clostridium*	2.5–5.8 Mb	Nayfach and Pollard (2015), Bull and Plummer (2014), and Bäckhed et al. (2012)
Skin	*Firmicutes, Proteobacteria, Bacteroides, Actinobacteria, Corynebacterium* spp., *Staphylococcus* spp., *Propionibacteriun* spp., *Malassezia* spp., *Cryptococcus* spp., *Epiciccum* spp., *Aspergillus* spp., and *Rhodotorula* spp. Gram negative organism abundance	2.23 Mb	Grice and Segre (2011), Ross et al. (2017), and Byrd et al. (2018)
Respiratory system	**URT:** *Staphylococcus* spp., *Corynebacterium* spp., *Propionibacterium* spp., *Moraxella* spp., *Streptococcus* spp. and *Dolosigranulum* spp. *Haemophilus* spp., *Rothia* spp., *Neisseria* spp., *Streptococcal* spp., *Veillonella* spp., *Leptotrichia* spp., *Prevotella* spp., *Penicillium* spp., *Candida* spp., *Aspergillus* spp., and *Alternaria* spp., human bocavirus, human adenovirus, human rhinovirus, human coronavirus, polyoma viruses and other *Anelloviridae* family		Nayfach and Pollard (2015), Man et al. (2017), Faner et al. (2017), Moffatt and Cookson (2017), Dickson et al. (2016), and Yatera et al. (2018)
	LRT: *Acinetobacter* spp., *Staphylococcus* spp. and *Ureaplasma* spp., *Haemophilus* spp., *Moraxella* spp., *Streptococcus* spp., *Staphylococcus* spp., *Tropheryma whipplei,* bacteriophages, *Anelloviridae, Systenosterma, Erethecium* and *Malassezia* genera		

(continued)

Table 20.1 (continued)

Site	Name of dominant species	Average genome size	References
Cardiovascular system	*H. pylori,* herpes simplex virus, *Cytomegalovirus, Chlamydia pneumoniae, Mycoplasma pneumoniae*, *Epstein Barr virus*	–	Clifford and Hoffman (2015)
Urinary system	*Corneybacterium, Escherichia, Ureaplasma, Mycoplasma, enterococcus, Aerococcus, Staphylococcus, Gemella, Anaerococcus, Prevotella*, *Finegoldia*., *Actinobaculum, Aerococcus, Anaerococcus, Gardnerella, Bulkholderia, Corneybacterium, Bifidobacterium, Actinobacteria, Bacteroidetes, Rhodobacter, Alloscardovia, Trueperella, Atopobium, Sneathia, Enterobacteriaceae, Shigella*, *Prevotella*., *Saccharofermentans, Proteiniphilum, Parvimonas* and *Jonquetella*	2.11 Mb	Nayfasch and Pollard (2015)

tract without the invasive techniques such as bronchoscopy. Hence, there has been a delay in the systemic microbiome assay until the first study indicating the similarity of bacterial density of this part with the upper small bowel of human body was reported (Man et al. 2017). This has been made possible due to the advances in molecular techniques independent of culture practices (Faner et al. 2017). Human respiratory system is divided into upper respiratory tract (URT) and lower respiratory tract (LRT) with alveoli, present in the LRT, acquiring the surface area nearly 70 m^2 (Man et al. 2017). This complete tract is occupied by the niche-specific microbiota with higher density dwelling in URT.

The development of microbiota has been thought to effect on the morphological genesis of this system (Man et al. 2017). During the first hours of a healthy neonate, non-specific microbes, presumed of maternal origin has been detected. Abundance of *Staphylococcus* spp. in the first week, in the URT due to niche specification, has also been detected, which is then occupied by the *Corynebacterium* spp., dominated by the *Dolosigranulum* spp. The *Moraxella* species has its dominance at the age of 4–6 months. The individuals with the possession of such microbiota have been found to possess stable microbiome community along with better airway health (Morris et al. 2013; Segal et al. 2013) This healthy development is prone to

disturbance under certain conditions such as usage of antibiotics, oxygen tension, temperature and pH, presence of other siblings, seasonal variations, vaccinations, exposure to smoke and host genetics (Man et al. 2017). Attempt to observe the diversity of flora in URT and LRT is well observed (Table 20.1).

20.2.3 The Microbiome of the Cardiovascular System

Studies using species specific molecular techniques have declared that the disease-free arteries and veins are microbe free in nature (Jin et al. 2019; Sobol 2014). Very few studies do report the presence of bacterial and viral genome in some vessels of healthy subjects. Amongst the microbes, *Helicobacter pylori* and herpes simplex virus are the most prevalent followed by *Cytomegalovirus, Chlamydia pneumoniae, Mycoplasma pneumoniae* and *Epstein Barr virus* and were also detected in healthy aorta, saphenous veins and internal mammary arteries (Clifford and Hoffman 2015).

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20.2.5 Urogenital Microbiome

The human urinary tract along with urine was earlier considered to be ‘sterile’, until the modern-day research, which has confirmed the presence of microbes in this system, significantly in healthy individuals. The advances in techniques such as 16 s rRNA sequencing have considerably helped in revealing the normal microbiota of the human body system. After analysis of the urine, the most common genera reported are *Lactobacillus* (more in women) and *Streptococcus* (more in men), both of which, along with few other groups, deliver a protective role in this system against different pathogens. Various bacterial taxa, as illustrated (Table 20.1), had been recognised in healthy adults, but some specific genera such as *Saccharofermentans, Proteiniphilum, Parvimonas* and *Jonquetella* were found in persons with age more than 70 years. The variation of urinary microbiome related to age and sex may be due to differences in voiding habits, hygiene, urinary metabolites, anatomic structures, hormonal variation and histology. Even the vaginal microbiome at premenstrual phase, reproductive age and post-menopausal phase exhibits variation (Aragón et al. 2018).

20.2.6 The Microbiome of the Nervous System

Central nervous system is considered to be one of the most immune privileged systems because of its closed compartmentalisation. It is isolated by physical barriers like blood-brain barriers and blood-cerebrospinal fluid barriers, from the circulatory system (Obermeier et al. 2013; Ransohoff and Engelhardt 2012). Thus, lack of lymphatic drainage, expression of major histocompatibility complex by the parenchymal cells and anti-inflammatory environment of the central nervous system accounts for such privileged status of seclusion from the microbiota (Berer and Krishnamoorthy 2014).

Though, in our body, there exists a bidirectional communication system, involving hormonal, immunological and neural signalling pathways, between the brain and the gut, accessed by the microbial flora of the intestine and certain metabolites, also known as the gut-brain axis. It is estimated that nearly 90% of serotonin (5-HT), a neurotransmitter, is produced in the intestine under the influence of gut microbiota, and the activation of its receptors in the enteric nervous system is responsible for the neuroprotection and adult neurogenesis in the mouse model (De Vadder et al. 2018).

20.2.7 The Microbiome of the Skin

The largest organ forming the external interface of the human body to the environment is the skin. Nearly 1.5–2.0 m^2 of the skin covers an average human with 2–3 mm depth. Three tissue layers are found in the skin: epidermis, dermis and hypodermis. Epidermis is colonised by millions of the microbes such as bacteria, fungi, arthropods and even viruses. It acts as the physical, anatomical and immunological barrier to various pathogens extending protection of the body, unless this barrier is broken or there is an imbalance between commensal and pathogenic organisms resulting to cutaneous or systemic diseases. Their acidic pH, continuous shedding of epidermal cells, hydrophobic nature, salinity and association with the antimicrobial compounds make them an efficient barrier (Ross et al. 2017). Though microbes do exist on them in spite of the above characteristics, the number of microbes inhabiting the skin ranges from one million to about one billion in each cm^2. Although, human skin is inhabited by quite diverse microflora, but most commonly found bacterial phyla includes *Proteobacteria, Corynebacteria, Propionibacteria, Bacteroidetes, Firmicutes and Staphylococcus* spp. Amongst fungi, *Malassezia* spp., *Cryptococcus* spp., *Epiciccum* spp., *Aspergillus* spp. and *Rhodotorula* spp. are most commonly found. The factors that affect the prevalence and dominance of community on the skin include biological sex, skin depth, skin location (skin thickness, folds, density of hairs), age, health, geographical location, ethnicity, use of lotions, soaps, cosmetics, and antibiotics and hygiene practices.

20.3 Influence of Microbiome on Human Health

As humans are known to have a constant symbiosis with microorganisms, the human microbial community, inhabiting the various system exhibits their influence on them. There are nearly 100 trillion symbiotic microorganisms that exist on and within the human body and have shown to play very important roles both in human health and disease causation. The influence of this microbiome on various systems is as follows:

20.3.1 Influence of Microbiome on Maintenance of Human-Gut Environment

Amongst all the systems, the highest and heterogeneous microbial density resides in colon and is mostly codependent in nature and present along both longitudinal (proximal to distal) and axial (mucosal to lumen) gradients of the gastrointestinal (GI) tract. The microbiome has been reported to aid in food digestion, vitamin biosynthesis, bile acid biotransformation, building of innate immunity, maintenance of intestinal barrier (Valdes et al. 2018), etc. Thus, gut is an "essential organ", carrying approximately 150 times more genes than are found in the entire human genome (Wang et al. 2017) (Fig. 20.1).

20.3.1.1 Metabolism

Microbial inhabitants within the host often contribute to metabolism such as:

- Bile salt metabolism
- Synthesis of essential and non-essential amino acids
- Replication of virulence factors in enteric pathogen
- Pro-drug transformation into active drugs and
- Metabolism of xenobiotic compounds
- Antibiotics by chemical transformation (Sarkar et al. 2018)

Gut microbiota and host interaction result in the secretion of a series of metabolites including trimethylamine-N-oxide (TMAO); short-chain fatty acid (SCFA) such as acetate and butyrate; secondary bile acid; and indoxyl sulphates that activate numerous signalling pathways affecting host physiological processes (Jin et al. 2019).

20.3.1.2 Contribution Towards the Host Immune System

When a child is born, the immune system at birth is under a relative state of immaturity. The developing immune system is characterised by a skewed T- and B-cell development and a blunted inflammatory cytokine production with respect to the regulatory responses. The consequence of such an underdeveloped immune system is high susceptibility to infections. Thereby, the regulatory environment ensures the establishment of the microbiota which ultimately helps in immune

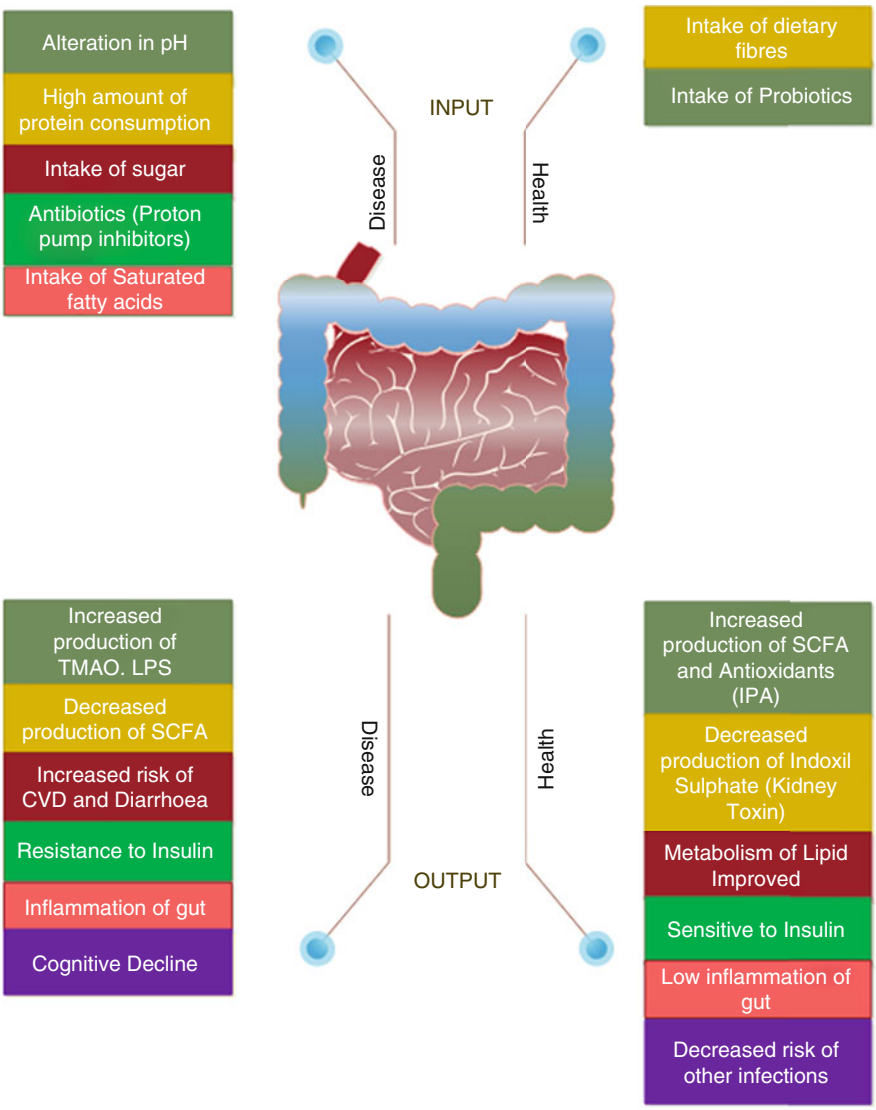

Fig. 20.1 Schematic diagram showing the role of the gut microbiota in health and disease with some inputs and outputs. *CVD* cardiovascular disease, *IPA* indole propionic acid, *LPS* lipopolysaccharide, *SCFA* short-chain fatty acids, *TMAO* trimethylamine-N-oxide

regulation and limits the mucosal inflammation following their colonisation (Elahi et al. 2013).

Many intestinal bacteria also prevent the colonisation of pathogen by producing antimicrobial substances such as bacteriocin (inhibit pathogen growth), by competing for nutrition and attachment sites. This act is termed as barrier/competitive-

exclusion effect (Collado et al. 2010). Exposure to intestinal bacteria has also been found to prevent certain allergic responses in the hosts.

Thereby, the commensals, specifically the bacterial species and the products or metabolites derived from them, are considered as an intrinsic regulator of all the immune responses for the upliftment and restoration of human meta-organism's health (Belkaid and Hand 2014).

20.3.1.3 Gut Microbiota and Associated Diseases

Gut bacteria are intrinsically linked with the health of our entire body. However, a change in gut microbiota composition, termed as dysbiosis, can result in enhanced susceptibility of the host towards pathology. Dysbiosis can cause various diseases such as inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS), chronic kidney disease (CKD), cardiovascular disease (CVD), atherosclerosis, obesity, autism, allergy, asthma, hypertension, coronary artery disease, and heart failure (Tang and Hazen 2017; Backhed, et al., 2012).

20.3.1.3.1 Irritable Bowel Syndrome (IBS) and Inflammatory Bowel Disease (IBD)

IBS and IBD are related to bowel disorder with signs and symptoms of abdominal cramping, pain and bloating associated with features of disordered defecation in IBS and ongoing inflammation of all part of GI tract in IBD. Although IBS is a multifactorial disease (Soares 2014), intestinal dysbiosis has also been found associated with this disease by facilitating adhesion of enteric pathogens. IBD includes Crohn's disease (CD) and ulcerative colitis (UC). Gut microbiota has been implicated to have roles in IBD pathogenesis, and the usage of antibiotics may help in reducing inflammation or prevented the same in murine models of disease and in patients.

20.3.1.3.2 Chronic Kidney Disease (CKD)

Intestinal dysbiosis is most often accompanied by defective intestinal barrier function, which promotes the production of bacterial by-products that are rapidly absorbed and retains in intestinal lumen. When increased absorption is coupled with reduced clearance of these substances by the kidneys, levels of gut derived toxins rise in circulation and may potentiate vascular calcification, atherosclerosis and adverse cardiovascular functioning, which are the clinical conditions in the later stage of CKD. Numerous epidemiologic studies have shown a relationship between gut-derived vascular toxins and cardiovascular events in patient with CKD (Valdes et al. 2018).

20.3.1.3.3 Gut Microbiome–Associated Cardiovascular Disease (CVD)

Metabolic origin of traditional CVD risk factors such as obesity, dyslipidaemia and insulin resistance indicates close linkage between the gut microbiome and CVD. Recent studies have implicated that atherosclerosis has generated the largest amount of data in association with gut microbiome. According to a hypothesis, gut microbiota metabolites elicit inflammatory cascade by translocating into

bloodstream and promote atherosclerosis. Oral bacteria causing oral cavities have also been found in atherosclerosis plaque (Clifford and Hoffman 2015). In many CVDs, heart failure is considered as end stage with a higher rate of morbidity and mortality (Jin et al. 2019). Low intestinal perfusion and disruption of intestinal barrier have been reported as reasons for reduced cardiac output and blood redistribution. The translocation of microbiota and endotoxins into blood circulation leads to an aggravated systemic inflammation that further can lead to increased chances of heart failure (Peng et al. 2018).

Various studies suggested the direct and indirect link between gut microbiota and the development of hypertension (Jin et al. 2019). It is a complex clinical condition and can be influenced by number of factors. It is considered as modifiable risk factor for CVD. In some studies, *Prevotella, Faecalibacterium, Klebsiella, Clostridium* and *Streptococcus* are found in abundance in hypertensive patients, indicating a close association of host microflora to such a clinical condition. Other studies demonstrated that reduction in gut microbial diversity, short-chain fatty acid (SCFA)-producing bacteria and increase in sympathetic drive to the gut and lactic acid producing bacteria, respectively, have direct role in blood pressure regulation. Thus, it can be concluded that blood pressure is closely linked to diversity, richness and evenness of microbiome living in the gut and the improved gut microbiota may be a target for future therapies for hypertension (Peng et al. 2018).

20.3.1.3.4 Human Nervous System Association with Gut Microbiota

The gut-brain axis plays a major role in central nervous system (CNS) and intestinal and immune system functioning, as mentioned earlier. Gut-brain axis is the bidirectional biochemical signalling between GI and CNS activities, integrating efferent and afferent neural, endocrine, nutrient and immunological signals, providing gut microbiota and its derived metabolites a route to access the brain (Bull and Plummer 2014; Joscelyn and Kasper 2014). Wang and Kasper illustrated that this bidirectional communication system enables brain to command GI functions such as metabolism, peristalsis, mucin production and other immunological functions.

Gut microbiota is also found to have impact on hypothalamic-pituitary-adrenal (HPA) axis, thus playing a role in body's stress response (Gareau et al. 2008; Teitelbaum et al. 2008). The gut microbiota has also been shown to synthesise neurotransmitters and neuromodulators. Various neurotransmitters produced by bacterial species are presented in Table 20.2. Those released neurotransmitter then stimulates epithelial cells to synthesise modulators within the enteric nervous system (ENS) or directly acting on primary afferent axons (McVey Neufeld et al. 2013). Moreover, it has been shown that ENS plays a major role in fundamental gastrointestinal physiological functions such as motility, fluid secretions and blood flow. Furthermore, numerous studies have revealed the correlation between microbiome, microbiota derived products, antibiotics, prebiotics and probiotics and CNS (Wang and Kasper 2014).

Anxiety and stress, characteristic mood disorders, associated with nervous, endocrinal and immunological system have also been shown to have an association with the gut microbiota. Stressors such as chemical, biological or any environmental

Table 20.2 Various neurotransmitters synthesised by different bacterial species

Bacterial species	Neurotransmitter
Lactobacillus spp.	Gamma-amino butyric acid (GABA), acetylcholine
Bifidobacterium spp.	Gamma-amino butyric acid (GABA)
Escherichia spp.	Norepinephrine (NE), 5-hydroxy tryptamine-serotonin (5-HT)
Bacillus spp.	Norepinephrine (NE), dopamine (DA)
Streptococcus spp.	5-HT
Enterococcus spp.	5-HT

stimuli can act as an active component to trigger the anxiety and stress response which ultimately activates the hypothalamic pituitary adrenal (HPA) axis. Intestinal dysbiosis and gut pathogens have thereby been shown to cause stress and anxiety. Animal models have represented to ameliorate these disorders by using probiotic formulations (Messaoudi et al. 2011). Various output and input of role of gut microbiota is depicted in Fig. 20.2.

20.4 Microbiome as a Paradigm for Future Nutritional and Medicinal Strategies

The analysis of microbiome of human body shows both the pathogenic as well as beneficial microbial network (Ozturk et al. 2017). Customizable medicine based on an individual's microbiome is an excellent approach for therapeutic choices based either on exercises or/and medications which considers the genetic makeup of an individual, their health condition and quality of life (Hasani-Ranjbar and Larijani 2017). Human genomes are about 99.9% indistinguishable to one another; the generally steady human gene pool does not completely clarify all the phenotypic varieties amongst people. On the other hand, the bacterial biological system, living in each human body, that contributes multiple times larger number of qualities than the human genome, could be significantly unique in relation to an individual. Therefore, the human microbiome can be regarded as the true cause of numerous responses that can influence the structure and plenitude of microorganism (Hasani-Ranjbar and Larijani 2017) in the human body.

Recently various studies have shown that intestinal microbiota is fundamentally associated with various therapeutics as in cardiovascular diseases, cancer, etc. These include narrow spectrum antibiotics along with probiotics, prebiotics and synbiotics, faecal microbiota transplantation, nutritional modulators, immune modulators and phage therapy.

20.4.1 Effects of Antibiotic Abuse on Microbiota

In the USA and Europe, jointly, in the year 2015, because of the onset of antibiotic resistance amongst pathogens, around 50,000 deaths were witnessed, which was

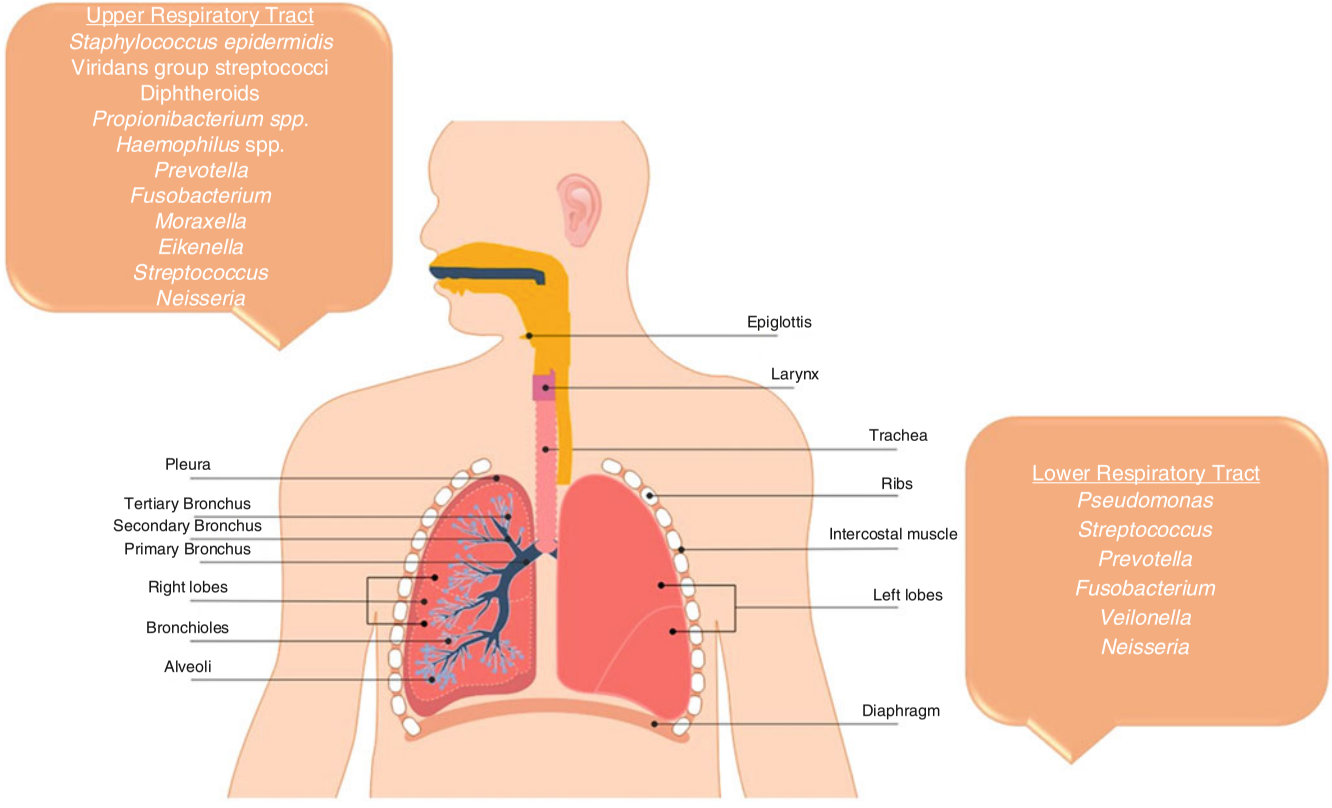

Fig. 20.2 Structures of human respiratory tract, the upper respiratory tract and the lower respiratory tract along with their prevalent microbiota

projected to increase to a score of around ten million deaths per year worldwide by 2050 (Langdon et al. 2016).

In addition to the development of resistance, the usage of antibiotics has been reported to disrupt the ecology of the human microbiome. Whereby, a dysbiotic microbiome loses the capability to perform vital functions such as nutrient supply, production of vitamin, and defence against the pathogens; thereby it leads to an eventual impairment of the metabolic, immunological and developmental system of the host. For an instance, drug-induced modification of the gut microflora can influence a group of $Foxp3^{+}$Treg cells that control demyelination in exploratory autoimmune encephalomyelitis (EAE) (Ochoa-Repáraz et al. 2010). Another study reflects the antigens produced by *Bacteroides fragilis* (capsule polysaccharide) can protect against EAE (CNS demyelination) and further in human multiple sclerosis (Ochoa-Repáraz et al. 2011). Similarly, the effects of common antimicrobial treatments on the gut microbiota have been illustrated in Table 20.3.

20.4.2 Probiotics

Probiotics are characterised as live microorganisms which are not part of the human host microbiome yet give a medical advantage to the host when administered or directed in sufficient quantity. Probiotics have been extensively studied in recent years as it imparts various health benefits by the metabolites it produces in the relief from certain intestinal disorders as well as controlling EAE. Clinical trials have been able to demonstrate that certain cardio metabolic disorders (CMD), such as type 2 diabetes mellitus (T2D), dyslipidaemia and arterial hypertension, as well as chronic kidney diseases (CKD) can be managed by the ingestion of probiotics (Neto et al. 2018). *Saccharomyces boulardii* has been shown to exert anti-inflammatory effect which helps to control inflammation related to the dysbiosis in lumen (Rodríguez-Nogales et al. 2018). Various metabolites produced by microorganisms present in the host and its associated health benefits are discussed in Table 20.4.

20.4.3 Prebiotics and Synbiotics

Prebiotics are those food components that cannot be digested by human body but can be selectively digested by the members of probiotics, and thereby serves as a food fibre for probiotics. Recent studies have demonstrated that the use of prebiotics can result in enhancing the ecological performance of the gut microbiota, thus promoting a much more beneficial community (Vandeputte et al. 2017). This conceptualizes that the human microbiota can be enhanced, stabilised and shifted by feeding with certain specific prebiotics such as carbohydrates. However, characterisation of the relationship between the prebiotic and probiotic is still a challenge. The point when the idea of synbiotic was first presented, two setups were proposed: first, where the prebiotic and probiotic segments were independent, each being in charge of a

Table 20.3 Effects of commonly used antimicrobials on gut microbiota

Antimicrobial class	Antimicrobial agent	Effects on faecal microbiota count			Reference
		Decrease in no. of microbiota	Increase in no. of microbiota	Constant no. of microbiota	
Penicillin	Piperacillin, tazobactum	*Bifidobacteria, Eubacteria, Lactobacilli, Enterobacter cloacae*	*Klebsiella pneumoniae*	Enterococci clostridia, Bacteroides	Morjaria et al. (2019) and Bhalodi et al. (2019)
	Ampicillin		*Enterobacter cloacae, Klebsiella pneumonia*		Kamal et al. (2019)
Cephalosporins	Cefuroxime	*Enterobacter cloacae*		*Klebsiella pneumoniae*	Kamal et al. (2019)
	Cefotaxime	Firmicutes, Actinobacteria, Bacteroidetes		Proteobacteria	Burdet et al. (2019)
	Ceftriaxone	Firmicutes, Actinobacteria, Bacteroidetes		Proteobacteria	Burdet et al. (2019)
Carbapenems	Meropenem		Actinobacteria Proteobacteria		Ye et al. (2019)
Fluoroquinolones	Ciprofloxacin			*Klebsiella pneumonia Enterobacter cloacae*	Kamal et al. (2019)
Aminoglycosides	Gentamicin		*Enterobacter cloacae*	*Klebsiella pneumoniae*	Kamal et al. (2019)

Table 20.4 Metabolites-producing microbiota and its associated health benefits

Microorganisms	Metabolites	Health benefits	References
Bacteroides fragilis	Polysaccharide A	Controls EAE and IBD by promoting $Foxp3^{+}$Treg quantity	Ochoa-Repáraz et al. (2010)
Lactobacilli Bifidobacteria	Lactic acid	Anti-inflammatory, promotes IL-$10^{+}Foxp3^{+}$Treg	Takata et al. (2011) and Kwon et al. (2013)
Escherichia coli	Vitamin B	Prevents vitamin K-deficiency bleeding, lower risk of type 2 diabetes	Tursunov et al. (2018), and Díaz-Rizzolo et al. (2019)
Bifidobacterium bifidum, Bifidobacterium longum, Bifidobacterium breve,	Complex vitamin B	Maintains the immune system, prevents cardiovascular diseases, chronic kidney diseases and improves nervous system	Yoshii et al. (2019), Sivamaruthi et al. (2019), Kobayashi et al. (2019), and Jena et al. (2018)
Bacteroides	Propionate and butyrate	Relieves from intestinal problems, relieves from tuberculosis	De Paepe et al. (2018) and Maji et al. (2018)
Propionibacteria	Propionate	Protects colon mucosa cells and prevents cancer, Prevent diarrhoea	Casanova et al. (2018) and Gaucher et al. (2019)
Veillonella, Bacteroides, Coprococcus, Lactobacillus, Ruminococcus	Acetate, lactate and propionate	Ecological performance of intestine is increased	El Hage et al. (2019)
Streptococcus thermophilus	Folic acid	Cures intestinal mucositis, has anti-cancer activity, promotes gut-bone signalling	Levit et al. (2018), Tarrah et al. (2018), and Schepper et al. (2017)

specific impact or medical advantage, and second, a symbiotic segment, where the probiotic was explicitly structured with a prebiotic substrate that would synergistically support the intensity, survival or metabolic movement of a related probiotic strain in the ecology of gastrointestinal system (Krumbeck et al. 2016).

As of late, two novel methodologies have been proposed for creating such synergistic synbiotics, both being dependent on their ecological function and wellness. First, the in vivo strategy which depends upon the determination and isolation of probiotic strain that would increase in number when a certain population of participants are administered with the specific prebiotic component (Krumbeck et al. 2015). Second, called as a multi-taxon insertion, depending on sequencing, based on the identification of genes, would examine the fitness of probiotic strain in relation to the type of prebiotic administered by the usage of libraries of transposon mutants (Wu et al. 2015). A list of prebiotics with their probiotic components are given in Table 20.5.

Table 20.5 List of prebiotic and its specific probiotic components

Prebiotic	Probiotic microorganisms	References
Inulin-type fructans	*Anaerostipes, Bilophila and Bifidobacterium*	Vandeputte et al. (2017)
Galacto-oligosaccharides	*Bifidobacterium*	Canfora et al. (2017)
Resistant Starch	*Bifidobacterium,* Proteobacteria	Alfa et al. (2018)
Xylooligosaccharide	*Blautia hydrogenotrophica; Bifidobacterium*	Long et al. (2019) and Carlson et al. (2017)
Whole fibre and pure inulin	Collinsella	Carlson et al. (2017)
Fructooligosaccharides	Lactobacillaceae; Bifidobacterium	Chen et al. (2017)

20.4.4 Faecal Microbiota Transplantation

Sometimes the mere usage of antibiotics is insufficient to treat few diseases and rather requires urgent alternatives to manage the severity of the clinical condition. This has led to the introduction of transplantation of the faecal microbiota. The process involves the separation and delivery of the faecal microbiota from stool of healthy donor to the gastrointestinal tract of the receiver patient, thereby enabling an efficient cure by normalising the microbiota composition. Recent investigations have explained the mechanism behind the faecal microbiota transplantation (FMT), which has been used to treat *Clostridium difficile* infection (CDI) for the restoration of the gut microbiome to gain the ability to inhibit *Clostridium difficile* indirectly by competing for nutrients. The faecal microbiota also prevents the colonisation by unwanted microorganism by the activation of immune system as well as by direct release of certain antimicrobial components and other metabolites that helps in the inhibition of vegetative and as well as the sporulated disease-causing organism (Khoruts and Sadowsky 2016). Table 20.6 shows the list of diseases and infections which can be treated by using FMT.

20.4.5 Nutritional Modulators

Intake of dietary medications for a long period of time impacts the structure and function of microbiome of the human body. The change in the availability of nutritional content of the diet causes corresponding alteration of the human microbiome. Recent findings have suggested that depending upon the intake of dietary, the microbiome richness diversifies. The lower is the genetic richness of microbiome; the lower will be the immune status of the person, relating to abnormal metabolic function and poor anti-inflammatory activity (Cotillard et al. 2013; Le Chatelier et al. 2013). The diet patterns may even contribute in managing different diseases (Table 20.7) by way of microbiome.

Table 20.6 Diseases and infections treated by FMT

Disease/infection	Mechanism	References
Clostridium difficile infection (CDI)	Competition for nutrients; direct suppression by antimicrobial peptides; bile-acid-mediated inhibition of spore germination and vegetative growth; activation of immune-mediated colonisation resistance	Khoruts and Sadowsky (2016)
Ulcerative colitis (UC)	Increasing the production of short-chain fatty acids, (butyrate); inhibitingTh1 differentiation, activity of T cells, leukocyte adhesion; production of inflammatory factors	Shen et al. (2018)
Irritable Bowel Syndrome (IBS)	Visceral hypersensitivity; altered barrier function, gastrointestinal motility and the gut-brain axis	Grover et al. (2014)
Obesity	Decrease adiposity; Alter metabolic phenotype by increased bacterial diversity	Marotz and Zarrinpar (2016)

Table 20.7 List of diseases that may be treated by dietary interventions

Diet pattern	Disease/infection	References
High fibre diet	Obesity	Menni et al. (2017)
	Ulcerative colitis	Silveira et al. (2017)
Fasting mimicking diet (FMD)	Multiple sclerosis and autoimmunity	Choi et al. (2016)
Calorie restriction	EAE	Piccio et al. (2008)
Sodium chloride restriction	Multiple sclerosis	Hernandez et al. (2015)
Western style diet	Anxiety	Ohland et al. (2013)
Poly unsaturated fatty acids	Depression	Gilbert et al. (2013)
Oestrogen	Breast cancer	Chen and Madak-Erdogan (2016)
Oleic acid	Ulcerative colitis	Fernández et al. (2020)
Polyphenols	Obesity	Henning et al. (2018)

20.4.6 Immune Modulators

Microbiome-based approaches involving antibiotics, probiotics, prebiotics and synbiotics, faecal microbiota transplantation and nutritional modulators correlate directly with the alteration of immune status of an individual focusing on the innate immunity. Thereby, the human microbiome is being affected for benefits with the change in immune status. Until now, there are inadequate information in this method; however, treatment of inflammatory diseases using steroids is in abundance. Intestinal innate and acquired immunity as well as systemic acquired immunity involves various mechanisms for the control of gut microbiome. Some of them include change in barrier function, expression of leptin, molecule β, human leukocyte antigen (HLA) class I and class II loci, activation of toll-like receptors, natural killer cells, CD4+ cells and Foxp3+ as well as the production of antimicrobial

peptides and α-defensins (Ticinesi et al. 2019) for the proper functioning of the gut microbiome.

20.4.7 Phage Therapy

Phage therapy involves the introduction of explicit bacteriophages that targets a microorganism which in turn has the ability to generate a beneficial microbiome shift. However, a limitation to this strategy is the simultaneous resistance offered by the microorganism in play which is yet to be proven. Till date, none of the phage therapy approaches have been established as an FDA-approved drug. Recently, scientists are working hard to perform phage based killing of microbes, but it is much more complicated. CRISPR (clustered regularly interspaced short palindromic repeats) is one of the approaches to advance the limitations (LeMieux 2019). It is a tool derived from prokaryotic immune system empowered to study and modify organisms with ease and efficiency. The system helps to modify the gut genome of gut microorganisms and bacteriophages. This engineered CRISPR-Cas system ultimately can control gene expression and modulate production of metabolite and protein presenting a new approach for the development of drugs that can target the microbiome (Table 20.8).

20.5 Conclusion

Although these interventions are used as medicinal and nutritional strategies and have been clinically experimented for a successful result, more focus and deliberate attempts are being made for the establishment of such casualty in order to define the functional metabolic change. These therapies are yet not so widely utilised due to the requirement of huge amount of money and time. Hence, advancement in this field targeting the relation of human microbiome with health and diseases, identification of the composition and activity of microbiome as well as linking it, and most importantly using technical resources such as bioinformatics to incorporate and fill up the loopholes ascertaining to the models is quite difficult. Future research based on these directions is a key to solve the problems and hence enlightening with knowledge about the human microbiome and their influence on the human health.

Table 20.8 Microbiome therapy involving CRISPR-Cas system

Therapy model	Microbiome therapy	References
Additive therapy	Probiotics (bacteria)	Hidalgo-Cantabrana et al. (2017)
	Probiotics (yeast)	Liu et al. (2016)
Subtractive therapy	Lytic phages	Hwang et al. (2018) and Yosef et al. (2015)
	Antimicrobials	Park et al. (2017)
Modulatory therapy	Temperate phages	Park et al. (2017) and Yosef et al. (2015)
	CRISPRi gene regulation	Berlec et al. (2018)

References

Alfa MJ, Strang D, Tappia PS, Graham M, Van Domselaar G, Forbes JD, Laminman V, Olson N, DeGagne P, Bray D, Murray BL (2018) A randomized trial to determine the impact of a digestion resistant starch composition on the gut microbiome in older and mid-age adults. Clin Nutr 37(3):797–807

Aragón IM, Herrera-Imbroda B, Queipo-Ortuño MI, Castillo E, Del Moral JS, Gómez-Millán J, Yucel G, Lara MF (2018) The urinary tract microbiome in health and disease. Eur Urol Focus 4 (1):128–138

Bäckhed F, Fraser CM, Ringel Y, Sanders ME, Sartor RB, Sherman PM, Versalovic J, Young V, Finlay BB (2012) Defining a healthy human gut microbiome: current concepts, future directions, and clinical applications. Cell Host Microbe 12(5):611–622

Belkaid Y, Hand TW (2014) Role of the microbiota in immunity and inflammation. Cell 157 (1):121–141

Berer K, Krishnamoorthy G (2014) Microbial view of central nervous system autoimmunity. FEBS Lett 588(22):4207–4213

Berlec A, Škrlec K, Kocjan J, Olenic M, Štrukelj B (2018) Single plasmid systems for inducible dual protein expression and for CRISPR-Cas9/CRISPRi gene regulation in lactic acid bacterium Lactococcus lactis. Sci Rep 8(1):1009

Bhalodi AA, van Engelen TS, Virk HS, Wiersinga WJ (2019) Impact of antimicrobial therapy on the gut microbiome. J Antimicrob Chemother 74(Supp 1):i6–i15

Breitbart M, Hewson I, Felts B, Mahaffy JM, Nulton J, Salamon P, Rohwer F (2003) Metagenomic analyses of an uncultured viral community from human feces. J Bacteriol 185(20):6220–6223

Bull MJ, Plummer NT (2014) Part 1: the human gut microbiome in health and disease. Integr Med Clin J 13(6):17

Burdet C, Grall N, Linard M, Bridier-Nahmias A, Benhayoun M, Bourabha K, Magnan M, Clermont O, d'Humières C, Tenaillon O, Denamur E (2019) Ceftriaxone and cefotaxime have similar effects on the intestinal microbiota in human volunteers treated by standard-dose regimens. Antimicrob Agents Chemother 63(6):e02244–e02218

Byrd AL, Belkaid Y, Segre JA (2018) The human skin microbiome. Nat Rev Microbiol *16*(3):143

Canfora EE, van der Bee CM, Hermes GD, Goossens GH, Jocken JW, Holst JJ, van Eijk HM, Venema K, Smidt H, Zoetendal EG, Dejong CH (2017) Supplementation of diet with galacto-oligosaccharides increases bifidobacteria, but not insulin sensitivity, in obese prediabetic individuals. Gastroenterology 153(1):87–97

Carlson J, Erickson J, Hess J, Gould T, Slavin J (2017) Prebiotic dietary fiber and gut health: comparing the in vitro fermentations of beta-glucan, inulin and Xylooligosaccharide. Nutrients 9(12):1361

Casanova MR, Azevedo-Silva J, Rodrigues LR, Preto A (2018) Colorectal cancer cells increase the production of short chain fatty acids by Propionibacterium freudenreichii impacting on cancer cells survival. Front Nutr 5

Chen KL, Madak-Erdogan Z (2016) Estrogen and microbiota crosstalk: should we pay attention? Trends in Endocrinol Metab 27(11):752–755

Chen D, Yang X, Yang J, Lai G, Yong T, Tang X, Shuai O, Zhou G, Xie Y, Wu Q (2017) Prebiotic effect of fructooligosaccharides from Morinda officinalis on Alzheimer's disease in rodent models by targeting the microbiota-gut-brain axis. Front Aging Neurosci 9:403

Chial H (2008) DNA sequencing technologies key to the Human Genome Project. Nature Education 1(1):219

Choi IY, Piccio L, Childress P, Bollman B, Ghosh A, Brandhorst S, Suarez J, Michalsen A, Cross AH, Morgan TE, Wei M (2016) A diet mimicking fasting promotes regeneration and reduces autoimmunity and multiple sclerosis symptoms. Cell Rep 15(10):2136–2146

Clifford A, Hoffman GS (2015) Evidence for a vascular microbiome and its role in vessel health and disease. Curr Opin Rheumatol 27(4):397–405

Collado MC, Gueimonde M, Salminen S (2010) Probiotics in adhesion of pathogens: mechanisms of action. In: Bioactive foods in promoting health. Academic, Chennai, pp 353–370
Costello EK, Lauber CL, Hamady M, Fierer N, Gordon JI, Knight R (2009) Bacterial community variation in human body habitats across space and time. Science 326(5960):1694–1697
Cotillard A, Kennedy SP, Kong LC, Prifti E, Pons N, Le Chatelier E, Almeida M, Quinquis B, Levenez F, Galleron N, Gougis S (2013) Dietary intervention impact on gut microbial gene richness. Nature 500(7464):585
De Paepe K, Verspreet J, Verbeke K, Raes J, Courtin CM, Van de Wiele T (2018) Introducing insoluble wheat bran as a gut microbiota niche in an in vitro dynamic gut model stimulates propionate and butyrate production and induces colon region specific shifts in the luminal and mucosal microbial community. Environ Microbiol 9:3406–3426
De Vadder F, Grasset E, Holm LM, Karsenty G, Macpherson AJ, Olofsson LE, Bäckhed F (2018) Gut microbiota regulates maturation of the adult enteric nervous system via enteric serotonin networks. Proc Natl Acad Sci 115(25):6458–6463
Díaz-Rizzolo DA, Kostov B, López-Siles M, Serra A, Colungo C, González-de-Paz L, Martinez-Medina M, Sisó-Almirall A, Gomis R (2019) Healthy dietary pattern and their corresponding gut microbiota profile are linked to a lower risk of type 2 diabetes, independent of the presence of obesity. Clin Nutr
Dickson RP, Erb-Downward JR, Martinez FJ, Huffnagle GB (2016) The microbiome and the respiratory tract. Annu Rev Physiol 78:481–504
Eckburg PB, Bik EM, Bernstein CN, Purdom E, Dethlefsen L, Sargent M, Gill SR, Nelson KE, Relman DA (2005) Diversity of the human intestinal microbial flora. Science 308 (5728):1635–1638
El Hage R, Hernandez-Sanabria E, Calatayud Arroyo M, Props R, Van de Wiele T (2019) Propionate-producing consortium restores antibiotic-induced dysbiosis in a dynamic in vitro model of the human intestinal microbial ecosystem. Front Microbiol 10:1206
Elahi S, Ertelt JM, Kinder JM, Jiang TT, Zhang X, Xin L, Chaturvedi V, Strong BS, Qualls JE, Steinbrecher KA, Kalfa TA (2013) Immunosuppressive CD71+ erythroid cells compromise neonatal host defence against infection. Nature 504(7478):158
Faner R, Sibila O, Agustí A, Bernasconi E, Chalmers JD, Huffnagle GB, Manichanh C, Molyneaux PL, Paredes R, Brocal VP, Ponomarenko J, Sethi S, Dorca J, Monsó E (2017) The microbiome in respiratory medicine: current challenges and future perspectives. Eur Respir J 49(4):1–12
Fernández J, García de la Fuente V, García MTF, Gómez Sánchez J, Redondo BI, Villar J, Lombó F (2020) A diet based on cured acorn-fed ham with oleic acid content promotes anti-inflammatory gut microbiota and prevents ulcerative colitis in an animal mode. Lipids Health Dis 19(28):1–19
Gao L, Xu T, Huang G, Jiang S, Gu Y, Chen F (2018) Oral microbiomes: more and more importance in oral cavity and whole body. Protein Cell 9(5):488–500
Gareau MG, Silva MA, Perdue MH (2008) Pathophysiological mechanisms of stress-induced Intestina damage. Curr Mol Med 8(4):274–281
Gaucher F, Bonnassie S, Rabah H, Marchand P, Blanc P, Jeantet R, Jan G (2019) Adaptation of beneficial Propionibacteria, lactobacilli, and Bifidobacteria improves tolerance toward technological and digestive stresses. Front Microbiol 10
Gilbert K, Arseneault-Bréard J, Monaco FF, Beaudoin A, Bah TM, Tompkins TA, Godbout R, Rousseau G (2013) Attenuation of post-myocardial infarction depression in rats by n-3 fatty acids or probiotics starting after the onset of reperfusion. Br J Nutr 109(1):50–56
Gill SR, Pop M, DeBoy RT, Eckburg PB, Turnbaugh PJ, Samuel BS, Gordon JI, Relman DA, Fraser-Liggett CM, Nelson KE (2006) Metagenomic analysis of the human distal gut microbiome. Science 312(5778):1355–1359
Grice EA, Segre JA (2011) The skin microbiome. Nat Rev Microbiol 9(4):244
Grover M, Camilleri M, Smith K, Linden DR, Farrugia G (2014) On the fiftieth anniversary Postinfectious irritable bowel syndrome: mechanisms related to pathogens. Neurogastroenterol Motil 26(2):156–167

Hasani-Ranjbar S, Larijani B (2017) Human microbiome as an approach to personalized medicine. Altern Ther Health Med 23(6):8–9

Henning SM, Yang J, Hsu M, Lee RP, Grojean EM, Ly A, Tseng CH, Heber D, Li Z (2018) Decaffeinated green and black tea polyphenols decrease weight gain and alter microbiome populations and function in diet-induced obese mice. Eur J Nutr 57(8):2759–2769

Hernandez AL, Kitz A, Wu C, Lowther DE, Rodriguez DM, Vudattu N, Deng S, Herold KC, Kuchroo VK, Kleinewietfeld M, Hafler DA (2015) Sodium chloride inhibits the suppressive function of FOXP3+ regulatory T cells. J Clin Invest 125(11):4212–4222

Hidalgo-Cantabrana C, O'Flaherty S, Barrangou R (2017) CRISPR-based engineering of next-generation lactic acid bacteria. Curr Opin Microbiol 37:79–87

Hwang IY, Lee HL, Huang JG, Lim YY, Yew WS, Lee YS, Chang MW (2018) Engineering microbes for targeted strikes against human pathogens. Cell Mol Life Sci 75(15):2719–2733

Jena PK, Sheng L, Nagar N, Wu C, Barile D, Mills DA, Wan YJ (2018) The effect of synbiotics Bifidobacterium infantis and milk oligosaccharides on shaping gut microbiota community structure and NASH treatment. Data Brief 19:1025–1029

Jin M, Qian Z, Yin J, Xu W, Zhou X (2019) The role of intestinal microbiota in cardiovascular disease. J Cell Mol Med 23(4):2343–2350

Joscelyn J, Kasper LH (2014) Digesting the emerging role for the gut microbiome in central nervous system demyelination. Mult Scler J 20(12):1553–1559

Kamal SS, Hyldig N, Krych Ł, Greisen G, Krogfelt KA, Zachariassen G, Nielsen DS (2019) Impact of early exposure to cefuroxime on the composition of the gut microbiota in infants following cesarean delivery. J Pediatr 210:99

Khoruts A, Sadowsky MJ (2016) Understanding the mechanisms of faecal microbiota transplantation. Nat Rev Gastroenterol Hepatol 13(9):508

Kobayashi Y, Kuhara T, Oki M, Xiao JZ (2019) Effects of Bifidobacterium breve A1 on the cognitive function of older adults with memory complaints: a randomised, double-blind, placebo-controlled trial. Benefic Microbes 10(5):511–520

Krumbeck JA, Maldonado-Gomez MX, Martínez I, Frese SA, Burkey TE, Rasineni K, Ramer-Tait AE, Harris EN, Hutkins RW, Walter J (2015) In vivo selection to identify bacterial strains with enhanced ecological performance in synbiotic applications. Appl Environ Microbiol 81 (7):2455–2465

Krumbeck JA, Maldonado-Gomez MX, Ramer-Tait AE, Hutkins RW (2016) Prebiotics and synbiotics: dietary strategies for improving gut health. Curr Opin Gastroenterol 32(2):110–119

Kwon HK, Kim GC, Kim Y, Hwang W, Jash A, Sahoo A, Kim JE, Nam JH, Im SH (2013) Amelioration of experimental autoimmune encephalomyelitis by probiotic mixture is mediated by a shift in T helper cell immune response. Clin Immunol 146(3):217–227

Langdon A, Crook N, Dantas G (2016) The effects of antibiotics on the microbiome throughout development and alternative approaches for therapeutic modulation. Genome Med 8(1):39

LaTuga MS, Ellis JC, Cotton CM, Goldberg RN, Wynn JL, Jackson RB, Seed PC (2011) Beyond bacteria: a study of the enteric microbial consortium in extremely low birth weight infants. PLoS One 6(12):e27858

Le Chatelier E, Nielsen T, Qin J, Prifti E, Hildebrand F, Falony G, Almeida M, Arumugam M, Batto JM, Kennedy S, Leonard P (2013) Richness of human gut microbiome correlates with metabolic markers. Nature 500(7464):541

LeMieux J (2019) Phage therapy: turning the tables on Bacteria: when engineered to incorporate CRISPR components, phages may overwhelm bacterial defenses or transform bacterial functions. Genet Eng Biotechnol News 39(3):20–22

Levit R, Savoy de Giori G, de Moreno de LeBlanc A, LeBlanc JG (2018) Folate-producing lactic acid bacteria reduce inflammation in mice with induced intestinal mucositis. J Appl Microbiol 125(5):1494–1501

Liu JJ, Kong II, Zhang GC, Jayakody LN, Kim H, Xia PF, Kwak S, Sung BH, Sohn JH, Walukiewicz HE, Rao CV (2016) Metabolic engineering of probiotic Saccharomyces boulardii. Appl Environ Microbiol 82(8):2280–2287

Long J, Yang J, Henning SM, Woo SL, Hsu M, Chan B, Heber D, Li Z (2019) Xylooligosaccharide supplementation decreases visceral fat accumulation and modulates cecum microbiome in mice. J Funct Foods 52:138–146

Maji A, Misra R, Dhakan DB, Gupta V, Mahato NK, Saxena R, Mittal P, Thukral N, Sharma E, Singh A, Virmani R (2018) Gut microbiome contributes to impairment of immunity in pulmonary tuberculosis patients by alteration of butyrate and propionate producers. Environ Microbiol 20(1):402–419

Man WH, de Steenhuijsen Piters WA, Bogaert D (2017) The microbiota of the respiratory tract: gatekeeper to respiratory health. Nat Rev Microbiol 15(5):259

Marotz CA, Zarrinpar A (2016) Focus: microbiome: treating obesity and metabolic syndrome with fecal microbiota transplantation. Yale J Biol Med 89(3):383

McVey Neufeld KA, Mao YK, Bienenstock J, Foster JA, Kunze WA (2013) The microbiome is essential for normal gut intrinsic primary afferent neuron excitability in the mouse. Neurogastroenterol Motil 25(2):183–e88

Menni C, Jackson MA, Pallister T, Steves CJ, Spector TD, Valdes AM (2017) Gut microbiome diversity and high-fibre intake are related to lower long-term weight gain. Int J Obes 41(7):1099

Messaoudi M, Lalonde R, Violle N, Javelot H, Desor D, Nejdi A, Bisson JF, Rougeot C, Pichelin M, Cazaubiel M, Cazaubiel JM (2011) Assessment of psychotropic-like properties of a probiotic formulation (Lactobacillus helveticus R0052 and Bifidobacterium longum R0175) in rats and human subjects. Br J Nutr 105(5):755–764

Moffatt MF, Cookson WO (2017) The lung microbiome in health and disease. Clin Med 17 (6):525–529

Morjaria S, Schluter J, Taylor BP, Littmann ER, Carter RA, Fontana E, Peled JU, van den Brink MR, Xavier JB, Taur Y (2019) Antibiotic-induced shifts in fecal microbiota density and composition during hematopoietic stem cell transplantation. bioRxiv 1:606533

Morris A, Beck JM, Schloss PD, Campbell TB, Crothers K, Curtis JL, Flores SC, Fontenot AP, Ghedin E, Huang L, Jablonski K (2013) Comparison of the respiratory microbiome in healthy nonsmokers and smokers. Am J Respir Crit Care Med 187(10):1067–1075

Nayfach S, Pollard KS (2015) Average genome size estimation improves comparative metagenomics and sheds light on the functional ecology of the human microbiome. Genome Biol 6(1):51

Neto MP, de Souza AJ, da Silva LD, de Oliveira SR, de Lima Guimaraes KS, de Oliveira Y, de Souza EL, Magnani M, Vidal H, de Brito Alves JL (2018) Gut microbiota and probiotics intervention: a potential therapeutic target for management of cardiometabolic disorders and chronic kidney disease? Pharmacol Res 130:152–163

Obermeier B, Daneman R, Ransohoff RM (2013) Development, maintenance and disruption of the blood-brain barrier. Nat Med 19(12):1584

Ochoa-Repáraz J, Mielcarz DW, Ditrio LE, Burroughs AR, Begum-Haque S, Dasgupta S, Kasper DL, Kasper LH (2010) Central nervous system demyelinating disease protection by the human commensal Bacteroides fragilis depends on polysaccharide A expression. J Immunol 185 (7):4101–4108

Ochoa-Repáraz J, Mielcarz DW, Begum-Haque S, Kasper LH (2011) Gut, bugs, and brain: role of commensal bacteria in the control of central nervous system disease. Ann Neurol 69(2):240–247

Ohland CL, Kish L, Bell H, Thiesen A, Hotte N, Pankiv E, Madsen KL (2013) Effects of Lactobacillus helveticus on murine behavior are dependent on diet and genotype and correlate with alterations in the gut microbiome. Psychoneuroendocrinology 38(9):1738–1747

Ozturk AB, Turturice BA, Perkins DL, Finn PW (2017) The potential for emerging microbiome-mediated therapeutics in asthma. Curr Allergy Asthma Rep 17(9):62

Park JY, Moon BY, Park JW, Thornton JA, Park YH, Seo KS (2017) Genetic engineering of a temperate phage-based delivery system for CRISPR/Cas9 antimicrobials against Staphylococcus aureus. Sci Rep 7:44929

Peng J, Xiao X, Hu M, Zhang X (2018) Interaction between gut microbiome and cardiovascular disease. Life Sci 214:153

Piccio L, Stark JL, Cross AH (2008) Chronic calorie restriction attenuates experimental autoimmune encephalomyelitis. J Leukoc Biol 84(4):940–948

Pothoulakis C (2009) Anti-inflammatory mechanisms of action of Saccharomyces boulardii. Aliment Pharmacol Ther 30(8):826–833

Ransohoff RM, Engelhardt B (2012) The anatomical and cellular basis of immune surveillance in the central nervous system. Nat Rev Immunol 12(9):623

Rodríguez-Nogales A, Algieri F, Garrido-Mesa J, Vezza T, Utrilla MP, Chueca N, García F, Rodríguez-Cabezas ME, Gálvez J (2018) Intestinal anti-inflammatory effect of the probiotic Saccharomyces boulardii in DSS-induced colitis in mice: impact on microRNAs expression and gut microbiota composition. J Nutr Biochem 61:129–139

Ross AA, Doxey AC, Neufeld JD (2017) The skin microbiome of cohabiting couples. MSystems 2 (4):e00043–e00017

Sarkar S, Das B, Banerjee SK (2018) Insights into the human gut microbiome and cardiovascular diseases. J Pract Cardiovasc Sci 4(1):10

Schepper JD, Irwin R, Kang J, Dagenais K, Lemon T, Shinouskis A, Parameswaran N, McCabe LR (2017) Probiotics in gut-bone signaling. In: Understanding the gut-bone signaling axis. Springer, Cham, pp 225–247

Segal LN, Alekseyenko AV, Clemente JC, Kulkarni R, Wu B, Chen H, Berger KI, Goldring RM, Rom WN, Blaser MJ, Weiden MD (2013) Enrichment of lung microbiome with supraglottic taxa is associated with increased pulmonary inflammation. Microbiome 1:19

Shen ZH, Zhu CX, Quan YS, Yang ZY, Wu S, Luo WW, Tan B, Wang XY (2018) Relationship between intestinal microbiota and ulcerative colitis: mechanisms and clinical application of probiotics and fecal microbiota transplantation. World J Gastroenterol 24(1):5

Silveira AL, Ferreira AV, de Oliveira MC, Rachid MA, da Cunha Sousa LF, dos Santos MF, Gomes-Santos AC, Vieira AT, Teixeira MM (2017) Preventive rather than therapeutic treatment with high fiber diet attenuates clinical and inflammatory markers of acute and chronic DSS-induced colitis in mice. Eur J Nutr 56(1):179–191

Sivamaruthi BS, Kesika P, Suganthy N, Chaiyasut C (2019) A review on role of microbiome in obesity and Antiobesity properties of probiotic supplements. BioMed Res Int 2019:1

Soares RL (2014) Irritable bowel syndrome: a clinical review. World J Gastroenterol *20*(34):12144

Sobol CV (2014) How microbiome impact on the cardiovascular system. J Clin Trial Cardiol 1:1411

Swidsinski A, Loening-Baucke V, Lochs H, Hale LP (2005) Spatial organization of bacterial flora in normal and inflamed intestine: a fluorescence in situ hybridization study in mice. World J Gastroenterol 11(8):1131

Takata K, Kinoshita M, Okuno T, Moriya M, Kohda T, Honorat JA, Sugimoto T, Kumanogoh A, Kayama H, Takeda K, Sakoda S (2011) The lactic acid bacterium Pediococcus acidilactici suppresses autoimmune encephalomyelitis by inducing IL-10-producing regulatory T cells. PLoS One 6(11):e27644

Tang WW, Hazen SL (2017) The gut microbiome and its role in cardiovascular diseases. Circulation 135(11):1008–1010

Tarrah A, De Castilhos J, Rossi RC, Duarte VD, Ziegler D, Corich V, Giacomini A (2018) In vitro probiotic potential and anti-cancer activity of newly isolated folate-producing Streptococcus thermophilus strains. Front Microbiol 9:2214

Teitelbaum AA, Gareau MG, Jury J, Yang PC, Perdue MH (2008) Chronic peripheral administration of corticotropin-releasing factor causes colonic barrier dysfunction similar to psychological stress. Am J Physiol Gastroint Liver Physiol 295(3):G452–G459

Thaiss CA, Zmora N, Levy M, Elinav E (2016) The microbiome and innate immunity. Nature 535 (7610):65–74

Ticinesi A, Lauretani F, Tana C, Nouvenne A, Ridolo E, Meschi T (2019) Exercise and immune system as modulators of intestinal microbiome: implications for the gut-muscle axis hypothesis. Exerc Immunol Rev 25

Tomayko E, Pillsbury L, Pray L (2013) The human microbiome, diet, and health: workshop summary. National Academies Press, Washington, DC

Turnbough L, Wilson L (2007) " Take your medicine": nonadherence issues in patients with ulcerative colitis. Gastroenterol Nurs 30(3):212–217

Tursunov D, Yoshida Y, Yrysov K, Sabirov D, Alimova K, Yamamoto E, Reyer JA, Hamajima N (2018) Estimated costs for treatment and prophylaxis of newborn vitamin K deficiency bleeding in Tashkent, Uzbekistan. Nagoya J Med Sci 80(1):11

Valdes AM, Walter J, Segal E, Spector TD (2018) Role of the gut microbiota in nutrition and health. BMJ 361:k2179

Vandeputte D, Falony G, Vieira-Silva S, Wang J, Sailer M, Theis S, Verbeke K, Raes J (2017) Prebiotic inulin-type fructans induce specific changes in the human gut microbiota. Gut 66 (11):1968–1974

Wang Y, Kasper LH (2014) The role of microbiome in central nervous system disorders. Brain Behav Immun 38:1–2

Wang B, Yao M, Lv L, Ling Z, Li L (2017) The human microbiota in health and disease. Engineering 3(1):71–82

Wu M, McNulty NP, Rodionov DA, Khoroshkin MS, Griffin NW, Cheng J, Latreille P, Kerstetter RA, Terrapon N, Henrissat B, Osterman AL (2015) Genetic determinants of in vivo fitness and diet responsiveness in multiple human gut Bacteroides. Science 350(6256):5992

Yatera K, Noguchi S, Mukae H (2018) The microbiome in the lower respiratory tract. Respir Investig 56(6):432–439

Ye L, Chan EW, Chen S (2019) Selective and suppressive effects of antibiotics on donor and recipient bacterial strains in gut microbiota determine transmission efficiency of bla NDM-1-bearing plasmids. J Antimicrob Chemother 74(7):1867–1875

Yosef I, Manor M, Kiro R, Qimron U (2015) Temperate and lytic bacteriophages programmed to sensitize and kill antibiotic-resistant bacteria. Proc Natl Acad Sci 112(23):7267–7272

Yoshii K, Hosomi K, Sawane K, Kunisawa J (2019) Metabolism of dietary and microbial vitamin B family in the regulation of host immunity. Front Nutr 6:48