



Interaction between diet composition and gut microbiota and its impact on gastrointestinal tract health

Muhammad Shahid Riaz Rajoka^a, Junling Shi^{a,*}, Hafiza Mahreen Mehwish^b, Jing Zhu^a, Qi Li^a, Dongyan Shao^a, Qingsheng Huang^a, Hui Yang^a

^a Key Laboratory for Space Bioscience and Space Biotechnology, School of Life Sciences, Northwestern Polytechnical University, Xi'an 710072, Shaanxi, People's Republic of China

^b Department of Biotechnology, University of Agriculture, Faisalabad, Pakistan

Received 15 May 2017; received in revised form 20 July 2017; accepted 26 July 2017

Available online 8 August 2017

Abstract

A substantial amount of emerging research is indicating that the gut microbiota has a significant impact on human health. Alterations of gut microbiota have clear consequences on intestinal homeostasis, physiology, gut microbiome, immune system and host metabolic pathways. Diet composition plays an important role in the control of gut microbial populations and, thus, in the prevention, management and treatment of certain diseases such as cancer, diabetes. A comprehensive analysis of previously reported results revealed that the gut microbiota can be modulated by diet and the composition of gut microbiota can be influenced by various diet components. The symbiotic relationship between different gut microbial communities regulates the immune system and, therefore, any dysbiosis can dysregulate the immune system. Further research is needed to fully understand the mechanisms involved in the interactions between diet composition, gut microbiota and associated diseases.

© 2017 Beijing Academy of Food Sciences. Production and hosting by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Keywords: Gut microbiota; Dysbiosis; Probiotics; Human health

1. Introduction

Over the past decades, the interaction between nutrition and the gut microbiota and its impact on human health has gathered increasing interest. Initial studies were primarily focused on the classification of microbial species forming the gut microbiota and the relationship of gut microbiota composition with the host health status [1]. Recent studies started to investigate the interaction between food and gut microbiota relative to the health of the host [2]. Current exciting research is beginning to unravel how the composition of food modulates the gut microbiota [3].

It has been found that the human-associated microbial communities are crucial for proper development of human and various hypotheses have been proposed to understand such relationship. One hypothesis is that the microbial communities of the mother affect fetal development and, consequently, the health of the offspring [4]. As a result, therapeutic interventions and diagnostic measurements which target the microbiota of the mother could prevent a negative impact on offspring health and premature birth [5]. Another assumption is that, after birth, the changing pattern of microbial populations relative to human development can be used to determine the importance of the microbiota in the development of individuals with healthy growth phenotypes. Therefore, it could be deduced that deviancies from normal microbial communities lead to abnormal development such as precocious maturation or immaturity [6].

The human body hosts at least 10^{14} microorganism and harbors more microbes than body cells [3,7]. All human-associated microbes are collectively known as microbiota and the microbiota encoding genes form the microbiome [6,8]. It is estimated

* Corresponding author.

E-mail address: sjlshi2004@nwpu.edu.cn (J. Shi).

Peer review under responsibility of Beijing Academy of Food Sciences.



Production and hosting by Elsevier

that the human gastrointestinal tract has 10 million genes which are associated with different microbial species and all genes have some beneficial impact on the health of the host, with possible effects on the homeostasis of the immune system, conversion of food into useful nutrients and protection against pathogenic microorganisms invading. However, due to the differences of diets, the microbiota differs widely from individual to individual and each person carries hundreds of microbial species that remain unchanged throughout adulthood [9–11].

The gut microbiota consists of bacteria, archaea, fungi, protozoa and viruses [12]. The microbial communities interact with each other and with their host, causing influence on the physiology and health of the host. The human gut microbiota is composed of both anaerobic and aerobic microbial communities [13]. Most gut microorganisms are strictly anaerobic bacteria and difficult to be cultured *in vitro*. At present, it is estimated that less than 30% of the gut microbial populations have been successfully cultured. However, this does not imply that all other bacterial species are unculturable, but rather that the optimal growth conditions for these microbes have not yet been discovered [14]. The development of high-throughput sequencing techniques has revolutionized the research process on currently uncultured microbes providing an insight into their mechanisms [15]. The dominant bacterial species in the human gastrointestinal tract are divided into three phyla: the phylum *Bacteroidetes* (e.g. *Porphyromonas*, *Prevotella* etc.), the phylum *Firmicutes* (e.g. *Ruminococcus*, *Clostridium*, *Eubacteria* etc.) and the phylum *Actinobacteria* (*Bifidobacterium*). Other bacteria such as *Lactobacilli*, *Streptococci* and *Escherichia coli* (*E.coli*) are found in small numbers. Based on the evidence from genomic technologies, the *Bacteroidetes* and *Firmicutes* phyla were found to be the dominant bacterial populations in the gastrointestinal (GI) tract (Fig. 1) [16,17].

The GI tract is currently reported to be sterile during gestation and become colonized after birth. Colonization of bacteria in the GI tract depends upon various factors such as type of childbirth and method of postnatal feeding [18]. The gut microbial population is transferred from mother to child and its composition is affected by various genetic factors [19,20]. The microbiota populations are also affected by diet and can be involved in the development of various diseases such as cancer, metabolic diseases and obesity. High-carbohydrate diets favor the *Prevotella* genus, whereas high-fat and high-protein diets promote the development of *Bacteroidetes* microbial species [21–23].

A disturbance in the interaction between nutrition, metabolism and microbiome may constitute an important factor in the deregulation of normal host homeostasis. Such disturbances in the structure and function of microbiota have been found to be related to the development of various diseases. It is, therefore, necessary to clearly define the range and composition of a normal, healthy microbiota. MetaHit and the Human Microbiome Project are conducting an in-depth analysis of the human-associated microbial communities and their function in maintaining the host homeostasis using various techniques [24–28].

After analyzing the currently available data, this review gives a comprehensive summary on the reports to illustrate how the

interaction between microbiota and food affects human physiology and, thus, generate useful information for the prevention of multiple diseases.

2. Impact of diet on GIT microbiota

Protein, fat and carbohydrates are the most common and major components in diets of human. The type and amount of protein, fat and carbohydrates present in the diet have been widely found to influence the composition of the gut microbiota in the host. This effect is related to the metabolites of the components present in diets. Short chain fatty acids, acetate and butyrate are reported as the end products of microbial-mediated degradation of protein and carbohydrates in the GI tract (GIT). Short chain fatty acids produced by GIT microbiota are the most extensively studied metabolites of diets and have been found to have a physiological effect on the health of the host [29].

Degradation of the protein in diets normally happens at the distal end of the colon, where the conditions are suitable for the secretion of proteolytic bacteria. The normal end products of protein degradation are amino acids, ammonia, amines and short chain fatty acids. High concentrations of ammonia have been found to be related to the development of malignant growths [30–33]. Gathered results showed that the rats feeding on diets consisting of protein isolated from whey cheese or containing cysteine or threonine resulted in a significant increase in bifidobacteria or lactobacilli counts in their feces [34–36]. Also of note, the protein isolated from whey cheese could alter the microbiota composition in a dose-dependent manner. Furthermore, it was observed that the mice that were fed high fat diets along with the whey-isolated protein tended to have an increase in *Lactobacillaceae* counts and a decrease in *Clostridiaceae* counts compared with the mice fed on a normal diet [37].

Dietary fiber is an important food component derived from plants. However, fiber concentration is lower in processed foods than in raw vegetables. Dietary fibers pass from the small intestine to the colon where they are partially metabolized by bacterial species and the remaining fibers are then excreted through feces. Some polysaccharides such as insulin, starch and oligosaccharides are the typical examples of dietary fibers which can be degraded by bacteria. However, certain fibers, such as cellulose, cannot be completely degraded by bacteria when passing through the colon [38]. In the GI tract, some carbohydrates, such as starch and non-starch polysaccharides, cannot be directly metabolized by the host. These complex carbohydrates normally act as an important energy resource for microbial growth and can be degraded by proteolytic enzymes into short chain fatty acids and various gases. These carbohydrates are also referred to as prebiotics that are defined as the non-digestible component of food that benefits the host by stimulating the growth of the microbiota. Prebiotics are very important to induce changes in the composition of the gut microbial populations and confer multiple benefits to the host health. Prebiotics such as insulin, fructooligosaccharides and oligosaccharides act as important stimulants which promote the growth of *bifidobacteria* and *lactobacilli* [39–41]. Recent studies indicate that the consumption of prebiotics can modu-

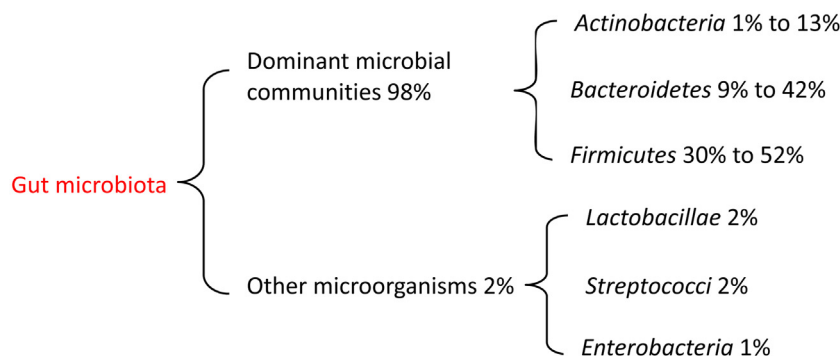


Fig. 1. Composition of gut microbiota.

late the gut microbial population and improve the hosts health [42].

It has been widely reported that the consumption of modern western diets containing less fiber and vegetables tended to result in the loss of some important microbial species in the western (urban) communities compared to rural communities. As previously mentioned, diets have a strong impact on the microbial diversity of individuals from different populations. For instance, when comparing an individual whose diet is high in fat and low in fiber with an individual on the opposite diet (e.g. high fiber and low fat), the latter tends to have a smaller amount of pathogenic bacteria and a large amount of beneficial microbes, such as *Prevotella* and *Xylanibacter* [43–45]. The balance of GIT microbial composition can be achieved as a result of symbiosis which regulates the immune system and protects the host from various diseases (Fig. 2).

The Mediterranean diet, which is based on a balanced intake of fruits, grains, monounsaturated fat, vegetables and polyunsaturated fats, is considered the standard for a healthy life style. It has been found that such diets have anti-inflammatory capabilities and can be used to reduce inflammation in diseases. Individuals fed on the Mediterranean diet have lower numbers of *Bacillaceae*, *Proteobacteria* and acute phase C-reactive proteins, but higher *Clostridium* and *Bacteroidetes* populations [46,47]. Vegetarian diets are also recognized as healthy and benefic diets because they can protect the host from various chronic, metabolic and inflammatory disorders. Recent investigations showed that vegetarian diets could increase the number of *Faecalibacterium prausnitzii*, *Clostridium clostridioforme* and *Bacteroides Prevotella*, but decrease the ratio of *Clostridium cluster XIVa* species [48–50].

Small amounts of dietary fat can be digested and absorbed but some fat components cannot be metabolized and pass to the colon where they affect the microbial composition and are then excreted in feces. Consequently, the consumption of high-fat foods tends to induce substantial changes in the composition of GI tract microbiota [51,52]. Mice fed on high-fat diets have different microbiota composition from those that have been fed control or balanced diets [53]. High fat content and increased calorie consumption have the capability to induce changes in the microbial composition of the GI tract [54,55]. Table 1 highlights

the impact of various dietary components on host microbiota and health status.

It has been also found that the children feeding on vegetarian diets rich in plant-based polysaccharides, fibers and starches had a significant increase in the number of *Firmicutes*, *Xylanibacter*, *Bacteroidetes* and *Prevotella* compared with those consuming a carbohydrate rich European diet. Therefore, it was suggested that children should be provided with a plant-based polysaccharide rich diet which confers protection against inflammatory disease [44].

Currently, it is clear that the composition of the microbiota differs among individuals living in different geographic regions and also depends on the long-term diet pattern. However, further investigation is required to identify the effects of long term and short term dietary patterns on the microbiota composition.

3. Impact of GIT microbiota on various diseases

The GIT microbiota has recently become a major subject of clinical research. Various studies have described the role of microbiota in ameliorating liver disease, irritable bowel syndrome, chronic inflammation, constipation, food allergies and cancers [43,60–64]. The gut microbiota interacts with the lymphoid tissue and epithelium, and, thus, plays an important role in the regulation and development of the host defense system [65,66]. The gut microbiota is involved in the regulation of antimicrobial peptides, mucin gene expression and paracellular permeability of the paneth cells of the small intestine. Moreover, a healthy microbiota is necessary for the maturation of the B cells and T cells, and the maintenance of proper immunoglobulin levels in the serum [67–69]. Recent studies showed that several diseases might be associated with the change in composition and metabolic activities of gut microbiota [70–72]. Changes in the composition and function of GI tract microbiota have also been linked to aging, obesity, neurodevelopmental disorders, cirrhosis, cardiovascular diseases and cancer [73–83].

3.1. GIT microbiota and cancer prevention

The intestinal microbiota has been increasingly recognized to be involved in the pathogenesis of diseases, even some kind of

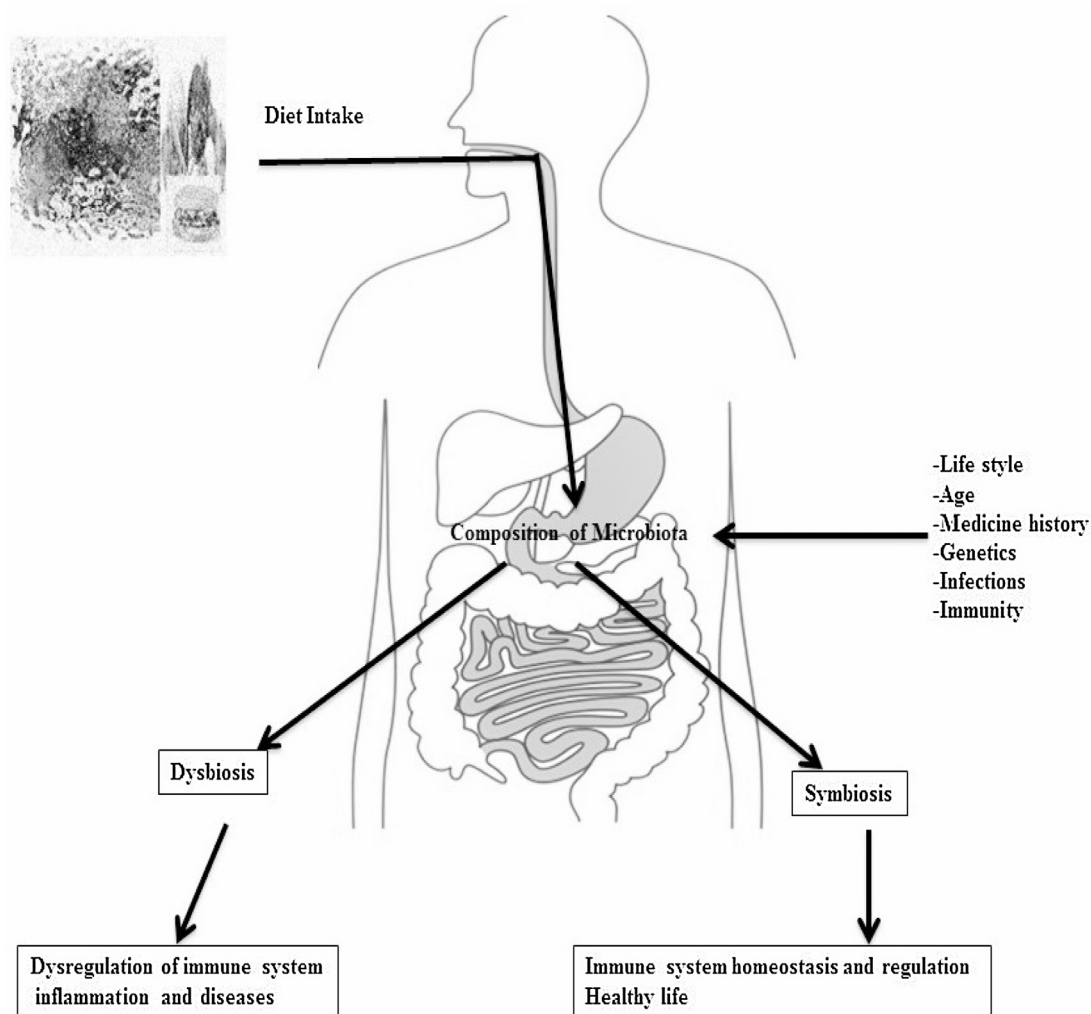


Fig. 2 Microbiota and homeostasis of the immune system.

Balance of GIT microbial composition could be achieved through symbiosis which regulates the immune system and protects the host from various diseases. Symbiosis could occur through the consumption of balanced diets. Dysbiosis, which could be caused by an imbalanced diet, dysregulates the immune system of the host which then becomes susceptible to inflammation and diseases.

Table 1
Influence of dietary components on host health and GIT microbiota.

Dietary component	Influence on microbiota	Influence on host health	Reference
Less vegetable, fish and fruits	Reduced microbiome [50]	Enhance of inflammation, triglyceride level, insulin resistance and low density lipoproteins cholesterol	[50]
Shift from vegetarian to animal centered diets	Enhances Enhanced <i>Bacteroides</i> and reduces reduced <i>Prevotella</i> counts [56]	Not fully understood	[56]
Low carbohydrate intake	Decreases Decreased <i>Eubacterium rectale</i> , <i>Bifidobacterium</i> and <i>Roseburia</i> species [52]	Not fully understood	[52]
High protein diet	Causes a rRiched <i>Bacteroides</i> associated enterotype, and decreases decreased <i>Firmicutes</i> [22,56]	Decrease in weight	[22,56]
Reduced food intake	Decreases Decreased overall microbial diversity [53]	Overall poor and declining heath	[53]
Western diet	Reduces Reduced <i>Bacteroidetes</i> and increases increased <i>Firmicutes</i> [57–59]	Inducing obesity	[57–59]
Plant-based, polysaccharide rich diet	Reduces Reduced <i>Firmicutes</i> and increases increased <i>Bacteroidetes</i> [59]	Increasing gut transit time	[59]

cancers [84]. It was supposed that the disturbance of GIT microbiota may promote carcinogenesis through three mechanisms: increasing bacterial translocation and consequently increasing inflammation, producing bacterial genotoxins that tend to induce DNA damage in organs, producing metabolites that can active carcinogens. The microbiota is also found to mediate tumor suppressive effects through inactivation of carcinogens, currently known as through the generation of short-chain fatty acids such as butyrate and through the biological activation of cancer-preventing phytochemicals [85]. Lactic acid bacteria are the most extensively reported components of GIT microbiota.

Various clinical studies have reported the effect of lactic acid bacteria (LAB) on preventing complication and alleviating symptoms of gastrointestinal cancer but LAB can also be used to inhibit intestinal carcinogenesis [86]. In the past year, various strains of LAB were reported to inhibit the proliferation and induce apoptosis of colon and gastric cancer cells as summarized in Table 2 [87]. Lactic acid bacteria (LAB) can be used for prevention of colon cancer due to their ability to modulate host immunity, intestinal microbiota, gut barrier function, anti-inflammatory and antipathogenic activity, and to suppress the bacterial translocation in the gut [88]. The beneficial effect of LAB is species specific, implying that different species have different effects on varying types of cancer. It is also suggested that the combination of two or more lactic acid bacteria might be more beneficial than a single LAB strain [88]. Concerning the mechanism of action of LAB, recent studies reported that such suppressive effect was dependent on short chain fatty acid production and upregulation of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) [89].

In addition, it was also reported that LAB are useful to treat cancer induced in various animal models through the administration of carcinogens, for example, azoxymethane. In one study, the administration of *Lactobacillus casei* BL23 protected the mice against colon cancer and facilitated the generation of T-helper Th-17-biased immune responses, as shown by the changes in cytokines levels and T-cells population. Furthermore, it was shown that the administration of *Pediococcus pentosaceus* GS4 suppresses the nuclear factor- κ B activity, which is associated with chronic cell proliferation and inflammation.

3.2. GIT microbiota and obesity

Obesity is a physiological state that arises in a population consuming western diets [92]. Obesity is linked to various metabolic disorders such as cardiovascular and liver diseases. The genetic makeup of the host, together with lifestyle and diet has been identified as major risk factors that tend to induce obesity. Common treatment options for obese individuals focus on decreasing the weight and include physical activity, calorie intake restriction and weight loss medication [93]. In obese hosts, the *Firmicutes* microbial population tends to increase, whilst the *Bacteroidetes* population tends to decrease [58]. However, a decrease in *Bacteroidetes* and an increase in the *Actinobacterium* population,

with normal levels of *Firmicutes* has recently been reported [74]. These microbial communities have a higher capacity to harvest food energy and produce low levels of inflammation. The decrease in microbiota composition in obese individuals is thought to be related to the reduction in insulin sensitivity and the stimulation of inflammation [23,74]. Research based on animal models found that host genetics and some environmental factors alter the microbiota composition and induce obesity [57,94]. The increase in harvesting food energy in the obese individuals is due to the hydrogen transfer between the microbiota phyla, since there is a consequent increase in hydrogen-using and hydrogen-producing microbes in those individuals [95]. The low level of chronic inflammation is found to be a major factor which causes obesity and enhances the level of macrophages, T cells, tumor necrosis factor, interleukin and mast cells [96].

In obese mice, *Bifidobacterium* species increase significantly and, thus, modulate the inflammation by producing glucagon peptide-2 and reducing lipopolysaccharide translocation [97]. The first finding demonstrating the role of microbiota in stimulating obesity came from a study that used germ free mice and showed the resistance to diets. Here, induced obesity depended on the macronutrient composition of the diets and improved the fat storage on microbiota colonization from the conventional donor [98–100].

Overall, the results of these studies indicate a link between dysbiosis and obesity, and suggest that the microbiota can enhance the host fat storage. However, the mechanisms responsible for the induction of obesity are very complex and still not completely understood.

3.3. GIT microbiota and type 2 diabetes

Type 2 diabetes alters the composition of gut microbiota and microbiota function such as the secondary metabolite bile acid and butyrate products. These functions are crucial for insulin sensitivity. The status of gut microbiota can be used to successfully distinguish between type 2 diabetes patients and healthy individuals in Chinese and European populations. Type 2 diabetes was linked to higher amounts of *Lactobacilli* and lower amounts of *Roseburia* when comparing the two populations [77,78,101–103]. However, the current understanding of the effect of GIT microbiota on type 2 diabetes is very limited. Further research is necessary to elucidate the interaction between the microbiota and the metabolism of the host, as well as to determine its impact on type 2 diabetes.

3.4. GIT microbiota and cardiovascular diseases

Cardiovascular diseases are the leading cause of death worldwide. The first indication of a link between GIT microbiota and cardiovascular diseases came from studies concerned with impaired dental health, cardiovascular diseases, infectious agents and atherosclerosis. Recent studies showed that certain bacterial strains used for the prevention of cardiovascular diseases exhibited antimicrobial activities [104–106]. Bacterial DNA identified from atherosclerotic plaques demonstrated the

Table 2
Effect of lactic acid bacteria on gastrointestinal cancer cells.

LAB	Cell lines	Results	Reference
<i>Pediococcus pentosaceus</i> GS4	HCT-116	Induction of apoptosis, proliferation inhibition and downregulation of NF-kB and p-Akt	[90]
<i>Kluyveromyces marxianus</i> YAS	Caco-2 and HT-29	Inhibition of cell proliferation, induction of apoptosis and upregulation of apoptosis-related genes	[91]
<i>Lactobacillus brevis</i> SBL8803	SW-620	Reduction of cell viability	[87]
<i>Lactobacillus plantarum</i> A7	Caco-2 and HT-29	Inhibition of cell proliferation	[84]
<i>Lactobacillus acidophilus</i> , <i>Lactobacillus casei</i> <i>Lactobacillus reuteri</i> NCIMB 701359	Caco-2	Inhibition of cell proliferation, reduction of migration and invasion ability	[88]
<i>Lactobacillus pentosus</i> B281, <i>Lactobacillus plantarum</i> B282	Caco-2 and SW-480	Induction of apoptosis, inhibition of proliferation	[57]
<i>Lactobacillus rhamnosus</i> , <i>Lactobacillus crispatus</i> <i>Lactobacillus paracasei</i> subsp. <i>paracasei</i> X12	Caco-2 and HT-29	Inhibition of cell proliferation	[81]
<i>Lactobacillus rhamnosus</i> , <i>Lactobacillus crispatus</i> <i>Lactobacillus paracasei</i> subsp. <i>paracasei</i> X12	HT-29	Inhibition of cell proliferation	[82]
<i>Lactobacillus casei</i> ATCC 393 <i>Lactobacillus reuteri</i>	HT-29 and CT-26 Caco-2	Arrest cell cycle through the regulation of mechanistic target of rapamycin (mTOR) signaling pathway Inhibition of cell proliferation Caused significant cytotoxicity in treatment of up to 72 h	[89] [84] [57,89]
<i>Lactobacillus fermentum</i>	Caco-2 and SW-480	Inhibition of cell proliferation	[84]

presence of a microbial load in the plaques which was, therefore, associated with influencing the development of cardiovascular diseases [107,108]. However, Metagenomic analysis of the fecal microbiome of healthy individuals and atherosclerosis patients showed a decrease in beta-carotene production gene (anti-inflammatory) and an increase in the peptidoglycan synthesis gene (proinflammatory) in the afflicted population [109].

3.5. GIT microbiota and parkinson's disease

Parkinson's disease is the most common neurodegenerative disease, affecting 1%–2% of the population over the age of 65 years. In recent decades, it was discovered that changes in neurodegenerative disorders occur through bidirectional communication in the gut-brain axis [110–112]. The gut-brain axis, or interaction, is developed during stress responses and it is believed that neuronal degeneration in conjunction with cognition and gastrointestinal disorders occur together. Hence, the neuro-hormonal factors and the gut microbiota influence the gut and brain function. It has been accepted that the gut microbiota influences the function of the central nervous system by establishing the pathway known as microbiota-gut-brain axis [113]. Dysfunctions in the microbiota-gut-brain axis result in the development of Parkinson's disease as evidenced by various disease symptoms [114,115]. Pain is experienced by approximately 45%–85% of Parkinson's disease patients. However, it has been noted that changes in the microbiota are associated with different types of pain such as migraines, autoimmune related pain, inflammatory pain and visceral pain in patients with rheumatoid arthritis [116–118]. The communication pathways are very complex involving neurochemical signaling molecules

which are used to facilitate this communication process. The gut microbiota stimulates the production of short-chain fatty acids and certain neurotransmitters. These factors contribute to the development of Parkinson's disease and the associated pains [119,120]. Therefore the microbiota has the potential to modulate the pain in Parkinson's disease patients.

4. Conclusions

Over the past decades, researchers have established a link between the alteration of gut microbial composition and various diseases. Diet affects the host health status by modulating the composition of the gut microbiota. It has been found that normal gut microbiota affects the development of the immune system, nutrient absorption, tissue generation, morphogenesis, and bone homeostasis metabolism. In this paper, we summarized the recent developments concerning the relationship between diseases and the gut microbiota. The modulation of the gut microbiota is a hot topic of interest and may benefit the health of the host (Fig. 3). However, there is still a substantial gap in our understanding of how diet modulates the microbiota and how microbiota modulates the immunity of the host. New tools and new approaches are needed for further investigations, as the modulation of the GIT microbiota represents a promising new method for the prevention, management and treatment of various diseases.

Disclosure statement

The authors declare that there are no conflicts of interest.

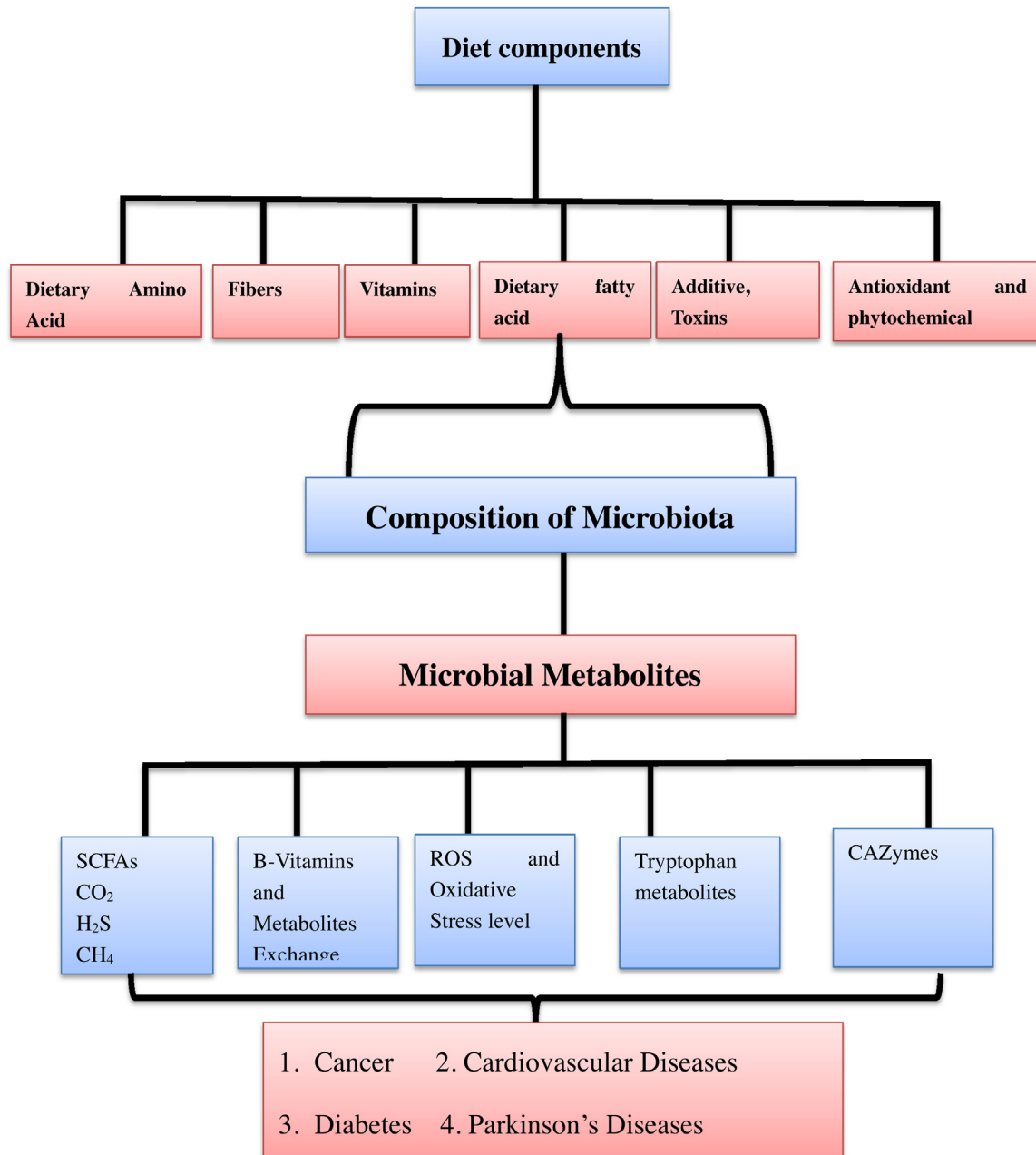


Fig. 3. Interaction between diet, Gut microbiota and host.

Acknowledgements

This study was supported by the National Key Technology R&D Program (grant number 2015BAD16B02) and the National Natural Science Foundation of China (NSFC) (grant number 31201408 and 31471718).

References

- [1] M.L. Hermannbank, K. Skovgaard, A. Stockmarr, N. Larsen, L. Mølbak, The Gut Microbiotassay: a high-throughput qPCR approach combinable with next generation sequencing to study gut microbial diversity, *BMC Genomics* 14 (2013) 788.
- [2] S. Prakash, C. Tomaroduchesneau, S. Saha, A. Cantor, The gut microbiota and human health with an emphasis on the use of microencapsulated bacterial cells, *BioMed Res. Int.* 2011 (2011) 1–12.
- [3] A.J. Bäuml, V. Sperandio, Interactions between the microbiota and pathogenic bacteria in the gut, *Nature* 535 (2016) 85–93.
- [4] Y. Sanz, Gut microbiota and probiotics in maternal and infant health, *Am. J. Clin. Nutr.* 94 (2011) 2000S–2005S.
- [5] M.C. Collado, M. Cernada, J. Neu, G. Pérezmartínez, M. Gormaz, M. Vento, Factors influencing gastrointestinal tract and microbiota immune interaction in preterm infants, *Pediatric Res.* 77 (2015) 726.
- [6] M.R. Charbonneau, L.V. Blanton, D.B. DiGiulio, D.A. Relman, C.B. Lebrilla, D.A. Mills, et al., A microbial perspective of human developmental biology, *Nature* 535 (2016) 48–55.
- [7] T. Shaheen, M. Siddiq, A. Nadeem, A. Hussain, F. Hayyat, J. Shi, In-vitro assessment of probiotic potential of lactic acid bacteria, *J. Biol. Today' World* 4 (2015) 190–198.

- [8] J. Wang, H. Jia, Metagenome-wide association studies: fine-mining the microbiome, *Nat. Rev. Microbiol.* 14 (2016) 508–522.
- [9] S.D. Ehrlich, Metagenomics of the intestinal microbiota: potential applications, *Gastroenterol. Clin. Biol.* 34 (2010) S23–S28.
- [10] C.A. Lozupone, J.I. Stombaugh, J.I. Gordon, J.K. Jansson, R. Knight, Diversity: stability and resilience of the human gut microbiota, *Nature* 489 (2012) 220–230.
- [11] L. Dethlefsen, P.B. Eckburg, E.M. Bik, D.A. Relman, Assembly of the human intestinal microbiota, *Trends Ecol. Evol.* 21 (2006) 517–523.
- [12] M.J. Claesson, I.B. Jeffery, S. Conde, S.E. Power, E.M. O'Connor, S. Cusack, et al., Gut microbiota composition correlates with diet and health in the elderly, *Nature* 488 (2012) 178.
- [13] R.D. Berg, The indigenous gastrointestinal microflora, *Trends Microbiol.* 4 (1996) 430–435.
- [14] M.H. Fraher, P.W. O'Toole, E.M. Quigley, Techniques used to characterize the gut microbiota: a guide for the clinician, *Nat. Rev. Gastroenterol. Hepatol.* 9 (2012) 312–322.
- [15] F. Fouhy, R.P. Ross, G.F. Fitzgerald, C. Stanton, P.D. Cotter, Composition of the early intestinal microbiota: knowledge gaps and the use of high-throughput sequencing to address these gaps, *Gut Microbes* 3 (2012) 203–220.
- [16] M.C. Collado, M. Cernada, C. B  ierl, M. Vento, G. P  rez-Mart  nez, Microbial ecology and host-microbiota interactions during early life stages, *Gut Microbes* 3 (2012) 352–365.
- [17] M. Breban, Gut microbiota and inflammatory joint diseases, *Joint Bone Spine* 83 (6) (2016) 645–649.
- [18] M.-M. Gr  lund, O.-P. Lehtonen, E. Eerola, P. Kero, Fecal microflora in healthy infants born by different methods of delivery: permanent changes in intestinal flora after cesarean delivery, *J. Pediatr. Gastroenterol. Nutr.* 28 (1999) 19–25.
- [19] J. Dor  , G. Corthier, The human intestinal microbiota, *Gastroenterol. Clin. Biol.* 34 (2010) S7–S15.
- [20] J.K. Goodrich, J.L. Waters, A.C. Poole, J.L. Sutter, O. Koren, R. Blekman, et al., Human genetics shape the gut microbiome, *Cell* 159 (2014) 789–799.
- [21] M. Arumugam, J. Raes, E. Pelletier, D. Le Paslier, T. Yamada, D.R. Mende, et al., Enterotypes of the human gut microbiome, *Nature* 473 (2011) 174–180.
- [22] G.D. Wu, J. Chen, C. Hoffmann, K. Bittinger, Y.-Y. Chen, S.A. Keilbaugh, et al., Linking long-term dietary patterns with gut microbial enterotypes, *Science* 334 (2011) 105–108.
- [23] E. Le Chatelier, T. Nielsen, J. Qin, E. Prifti, F. Hildebrand, G. Falony, et al., Richness of human gut microbiome correlates with metabolic markers, *Nature* 500 (2013) 541–546.
- [24] F. Sommer, F. B  ckhed, The gut microbiota—masters of host development and physiology, *Nat. Rev. Microbiol.* 11 (2013) 227–238.
- [25] H. Garn, J.F. Neves, R.S. Blumberg, H. Renz, Effect of barrier microbes on organ-based inflammation, *J. Allergy Clin. Immunol.* 131 (2013) 1465–1478.
- [26] D. Gevers, R. Knight, J.F. Petrosino, K. Huang, A.L. McGuire, B.W. Birren, et al., The Human Microbiome Project: a community resource for the healthy human microbiome, *PLoS Biol.* 10 (2012) e1001377.
- [27] K. Aagaard, J. Petrosino, W. Keitel, M. Watson, J. Katancik, N. Garcia, et al., The Human Microbiome Project strategy for comprehensive sampling of the human microbiome and why it matters, *FASEB J.* 27 (2013) 1012–1022.
- [28] X.C. Morgan, C. Huttenhower, Meta'omic analytic techniques for studying the intestinal microbiome, *Gastroenterology* 146 (2014) 1437–1448 (e1).
- [29] G.T. Macfarlane, S. Macfarlane, Bacteria colonic fermentation, and gastrointestinal health, *J. AOAC Int.* 95 (2012) 50–60.
- [30] A.W. Walker, S.H. Duncan, E.C.M. Leitch, M.W. Child, Flint HJ pH and peptide supply can radically alter bacterial populations and short-chain fatty acid ratios within microbial communities from the human colon, *Appl. Environ. Microbiol.* 71 (2005) 3692–3700.
- [31] G. Macfarlane, J. Cummings, C. Allison, Protein degradation by human intestinal bacteria, *Microbiology* 132 (1986) 1647–1656.
- [32] J. Cummings, G. Macfarlane, The control and consequences of bacterial fermentation in the human colon, *J. Appl. Bacteriol.* 70 (1991) 443–459.
- [33] H.M. Hamer, V. De Preter, K. Windey, K. Verbeke, Functional analysis of colonic bacterial metabolism: relevant to health? *Am. J. Physiol. Gastrointest. Liver Physiol.* 302 (2012) G1–G9.
- [34] E.A. Magee, C.J. Richardson, R. Hughes, J.H. Cummings, Contribution of dietary protein to sulfide production in the large intestine: an in vitro and a controlled feeding study in humans, *Am. J. Clin. Nutr.* 72 (2000) 1488–1494.
- [35] P.C. Elwood, D.I. Givens, A.D. Beswick, A.M. Fehily, J.E. Pickering, J. Gallacher, The survival advantage of milk and dairy consumption: an overview of evidence from cohort studies of vascular diseases diabetes and cancer, *J. Am. Coll. Nutr.* 27 (2008) 723S–734S.
- [36] R. Sprong, A. Schonewille, R. Van der Meer, Dietary cheese whey protein protects rats against mild dextran sulfate sodium?induced colitis: role of mucin and microbiota, *J. Dairy Sci.* 93 (2010) 1364–1371.
- [37] M. Guerville, G. Boudry, Gastro-intestinal and hepatic mechanisms limiting the entry and dissemination of lipopolysaccharide into the systemic circulation, *Am. J. Physiol. Gastrointest. Liver Physiol.* 311 (2016) G1–G15, <http://dx.doi.org/10.1152/ajpgi.00098.2016>.
- [38] M. Blaut, Relationship of prebiotics and food to intestinal microflora, *Eur. J. Nutr.* 41 (2002), i11–i6.
- [39] J.H. Cummings, H.N. Englyst, What is dietary fibre, *Trends Food Sci. Technol.* 2 (1991) 99–103.
- [40] F. Respondek, K.S. Swanson, K.R. Belsito, B.M. Vester, A. Wagner, L. Istasse, et al., Short-chain fructooligosaccharides influence insulin sensitivity and gene expression of fat tissue in obese dogs, *J. Nutr.* 138 (2008) 1712–1718.
- [41] G. Glenn, M. Roberfroid, Dietary modulation of the human colonic microbiota: introducing the concept of prebiotics, *J. Nutr.* 125 (1995) 1401–1412.
- [42] A.T. Vieira, M.M. Teixeira, FdS. Martins, The role of probiotics and prebiotics in inducing gut immunity, *Front. Immunol.* 4 (2013) 445.
- [43] S.L. Schnorr, M. Candela, S. Rampelli, M. Centanni, C. Consolandi, G. Basaglia, et al., Gut microbiome of the Hadza hunter-gatherers, *Nat. Commun.* 5 (2014).
- [44] C. De Filippo, D. Cavalieri, M. Di Paola, M. Ramazzotti, J.B. Poullet, S. Massart, et al., Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa, *Proc. Natl. Acad. Sci. U. S. A.* 107 (2010) 14691–14696.
- [45] J. Ou, F. Carbonero, E.G. Zoetendal, J.P. DeLany, M. Wang, K. Newton, et al., Diet microbiota, and microbial metabolites in colon cancer risk in rural Africans and African Americans, *Am. J. Clin. Nutr.* 98 (2013) 111–120.
- [46] G. Marlow, S. Ellett, I.R. Ferguson, S. Zhu, N. Karunasinghe, A.C. Jesuthasan, et al., Transcriptomics to study the effect of a Mediterranean-inspired diet on inflammation in Crohn's disease patients, *Hum. Genomics* 7 (1) (2013).
- [47] F. De Filippis, N. Pellegrini, L. Vannini, I.B. Jeffery, A. La Stora, L. Laghi, et al., High-level adherence to a Mediterranean diet beneficially impacts the gut microbiota and associated metabolome, *Gut* 65 (2016) 1812–1821, <http://dx.doi.org/10.1136/gutjnl-2015-309957>.
- [48] M. Glick-Bauer, M.-C. Yeh, The health advantage of a vegan diet: exploring the gut microbiota connection, *Nutrients* 6 (2014) 4822–4838.
- [49] I. Ferrocino, R. Di Cagno, M. De Angelis, S. Turrone, L. Vannini, E. Bancalari, et al., Fecal microbiota in healthy subjects following omnivore, vegetarian and vegan diets: culturable populations and rRNA DGGE profiling, *PLoS One* 10 (2015) e0128669.
- [50] B.B. Matija  i  , T. Obermajer, L. Lipoglav  ek, I. Grabnar, G. Avgu  tin, I. Rogelj, Association of dietary type with fecal microbiota in vegetarians and omnivores in Slovenia, *Eur. J. Nutr.* 53 (2014) 1051–1064.
- [51] L. Gabert, C. Vors, C. Louche-P  lissier, V. Sauvinet, S. Lambert-Porcheron, J. Dra  , et al., ¹³C tracer recovery in human stools after digestion of a fat-rich meal labelled with [1,1, 1-¹³C₃] tripalmitin and [1,1, 1-¹³C₃] triolein, *Rapid Commun. Mass Spectrom.* 25 (2011) 2697–2703.
- [52] E. Murphy, P. Cotter, S. Healy, T. Marques, O. O'sullivan, F. Fouhy, et al., Composition and energy harvesting capacity of the gut microbiota:

- relationship to diet, obesity and time in mouse models, *Gut* 59 (2010) 1635–1642.
- [53] H. Daniel, A.M. Gholami, D. Berry, C. Desmarchelier, H. Hahne, G. Loh, et al., High-fat diet alters gut microbiota physiology in mice, *ISME J.* 8 (2014) 295–308.
- [54] S.F. Clarke, E.F. Murphy, K. Nilaweera, P.R. Ross, F. Shanahan, P.W. O'Toole, et al., The gut microbiota and its relationship to diet and obesity: new insights, *Gut Microbes* 3 (2012) 186–202.
- [55] C. Zhang, S. Li, L. Yang, P. Huang, W. Li, S. Wang, et al., Structural modulation of gut microbiota in life-long calorie-restricted mice, *Nat. Commun.* 4 (2013).
- [56] L.A. David, C.F. Maurice, R.N. Carmody, D.B. Gootenberg, J.E. Button, B.E. Wolfe, et al., Diet rapidly and reproducibly alters the human gut microbiome, *Nature* 505 (2014) 559–563.
- [57] P.J. Turnbaugh, F. Bäckhed, L. Fulton, J.I. Gordon, Diet-induced obesity is linked to marked but reversible alterations in the mouse distal gut microbiome, *Cell Host Microbe* 3 (2008) 213–223.
- [58] R.E. Ley, F. Bäckhed, P. Turnbaugh, C.A. Lozupone, R.D. Knight, J.I. Gordon, Obesity alters gut microbial ecology, *Proc. Natl. Acad. Sci. U. S. A.* 102 (2005) 11070–11075.
- [59] W. Shen, H.R. Gaskins, M.K. McIntosh, Influence of dietary fat on intestinal microbes inflammation, barrier function and metabolic outcomes, *J. Nutr. Biochem.* 25 (2014) 270–280.
- [60] M.S. Riaz, T. Shaheen, N. Batool, S. Saleem, A. Haris, F. Hayat, et al., Modulation of immune system by taking probiotic bacteria: especially focus on lactic acid bacteria, *Asian J. Agric. Biol.* 3 (2) (2015) 74–77.
- [61] M. Ndagijimana, L. Laghi, B. Vitali, G. Placucci, P. Brigidi, M.E. Guersoni, Effect of a synbiotic food consumption on human gut metabolic profiles evaluated by ¹H Nuclear Magnetic Resonance spectroscopy, *Int. J. Food Microbiol.* 134 (2009) 147–153.
- [62] S. Sierra, F. Lara-Villoslada, L. Sempere, M. Olivares, J. Boza, J. Xaus, Intestinal and immunological effects of daily oral administration of *Lactobacillus salivarius* CECT5713 to healthy adults, *Anaerobe* 16 (2010) 195–200.
- [63] N. Pérez, J.C. Iannicelli, C. Girard-Bosch, S. González, A. Varea, L. Disalvo, et al., Effect of probiotic supplementation on immunoglobulins: isoagglutinins and antibody response in children of low socio-economic status, *Eur. J. Nutr.* 49 (2010) 173–179.
- [64] M. Baron, Original research: a patented strain of bacillus coagulans increased immune response to viral challenge, *Postgrad. Med.* 121 (2009) 114–118.
- [65] Y. Sanz, G. De Palma, Gut microbiota and probiotics in modulation of epithelium and gut-associated lymphoid tissue function, *Int. Rev. Immunol.* 28 (2009) 397–413.
- [66] B. Chassaing, O. Koren, J.K. Goodrich, A.C. Poole, S. Srinivasan, R.E. Ley, et al., Dietary emulsifiers impact the mouse gut microbiota promoting colitis and metabolic syndrome, *Nature* 519 (2015) 92–96.
- [67] H. Tlaskalová-Hogenová, R. Štěpánková, T. Hudcovic, L. Tučková, B. Cukrowska, R. Lodinová-Žádníková, et al., Commensal bacteria (normal microflora), mucosal immunity and chronic inflammatory and autoimmune diseases, *Immunol. Lett.* 93 (2004) 97–108.
- [68] C.A. Thaiss, N. Zmora, M. Levy, E. Elinav, The microbiome and innate immunity, *Nature* 535 (2016) 65–74.
- [69] M. Shahid Riaz, T. Shaheen, N. Batool, S. Saleem, F. Hayat, Lactic acid bacteria as probiotic candidate and their application, *J. Biol. Today's World* 4 (2015) 209–216.
- [70] F. Bäckhed, R.E. Ley, J.L. Sonnenburg, D.A. Peterson, J.I. Gordon, Host-bacterial mutualism in the human intestine, *Science* 307 (2005) 1915–1920.
- [71] J.F. Rawls, B.S. Samuel, J.I. Gordon, Gnotobiotic zebrafish reveal evolutionarily conserved responses to the gut microbiota, *Proc. Natl. Acad. Sci. U. S. A.* 101 (2004) 4596–4601.
- [72] C. Manichanh, L. Rigottier-Gois, E. Bonnaud, K. Gloux, E. Pelletier, L. Frangeul, et al., Reduced diversity of faecal microbiota in Crohn's disease revealed by a metagenomic approach, *Gut* 55 (2006) 205–211.
- [73] S. Subramanian, S. Huq, T. Yatsunenko, R. Haque, M. Mahfuz, M.A. Alam, et al., Persistent gut microbiota immaturity in malnourished Bangladeshi children, *Nature* 510 (2014) 417–421.
- [74] P.J. Turnbaugh, M. Hamady, T. Yatsunenko, B.L. Cantarel, A. Duncan, R.E. Ley, et al., A core gut microbiome in obese and lean twins, *Nature* 457 (2009) 480–484.
- [75] N. Qin, F. Yang, A. Li, E. Prifti, Y. Chen, L. Shao, et al., Alterations of the human gut microbiome in liver cirrhosis, *Nature* 513 (2014) 59–64.
- [76] J.M. Brown, S.L. Hazen, The gut microbial endocrine organ: bacterially-Derived signals driving cardiometabolic diseases, *Annu. Rev. Med.* 66 (2015) 343.
- [77] F.H. Karlsson, V. Tremaroli, I. Nookaew, G. Bergström, C.J. Behre, B. Fagerberg, et al., Gut metagenome in European women with normal: impaired and diabetic glucose control, *Nature* 498 (2013) 99–103.
- [78] J. Qin, Y. Li, Z. Cai, S. Li, J. Zhu, F. Zhang, et al., A metagenome-wide association study of gut microbiota in type 2 diabetes, *Nature* 490 (2012) 55–60.
- [79] N.W. Palm, M.R. De Zoete, T.W. Cullen, N.A. Barry, J. Stefanowski, L. Hao, et al., Immunoglobulin A coating identifies colitogenic bacteria in inflammatory bowel disease, *Cell* 158 (2014) 1000–1010.
- [80] J.P. Zackular, M.A. Rogers, M.T. Ruffin, P.D. Schloss, The human gut microbiome as a screening tool for colorectal cancer, *Cancer Prev. Res.* 7 (2014) 1112–1121.
- [81] E.Y. Hsiao, S.W. McBride, S. Hsien, G. Sharon, E.R. Hyde, T. McCue, et al., Microbiota modulate behavioral and physiological abnormalities associated with neurodevelopmental disorders, *Cell* 155 (2013) 1451–1463.
- [82] I.B. Jeffery, D.B. Lynch, P.W. O'Toole, Composition and temporal stability of the gut microbiota in older persons, *ISME J.* 10 (2015) 170–182.
- [83] J.L. Sonnenburg, F. Bäckhed, Diet-microbiota interactions as moderators of human metabolism, *Nature* 535 (2016) 56–64.
- [84] G. Trinchieri, Microbiome and cancer, *Semin. Immunopathol.* 37 (2015) 65.
- [85] R.F. Schwabe, C. Jobin, The microbiome and cancer, *Nat. Rev. Cancer* 13 (2013) 800–812.
- [86] M.B. Burns, J. Lynch, T.K. Starr, D. Knights, R. Blekhman, Virulence genes are a signature of the microbiome in the colorectal tumor microenvironment, *Genome Med.* 7 (2015) 55.
- [87] Y. Nami, B. Haghshenas, M. Haghshenas, N. Abdullah, A. Yari Khosroushahi, The prophylactic effect of probiotic enterococcus lactis IW5 against different human cancer cells, *Front. Microbiol.* 6 (2015) 1317.
- [88] A.Q. Yu, L. Li, The potential role of probiotics in cancer prevention and treatment, *Nutr. Cancer* 68 (2016) 535–544.
- [89] Hojjat Sadeghi-Aliabadi*, F. Mohammadi, Fazeli Hossain, Mirlohi Maryam, Effects of *Lactobacillus plantarum* A7 with probiotic potential on colon cancer and normal cells proliferation in comparison with a commercial strain, *Iran J. Basic Med. Sci.* 17 (2014) 815–819.
- [90] V. Dubey, A.R. Ghosh, K. Bishayee, A.R. Khuda-Bukhsh, Appraisal of the anti-cancer potential of probiotic *Pediococcus pentosaceus* GS4 against colon cancer: in vitro and in vivo approaches, *J. Funct. Foods* 23 (2016) 66–79.
- [91] Amir Saber Gharamaleki, B. Alipour, Zeinab Faghfoori, Ahmad YariKhosroushahi, Prophylactic effects of dairy *kluyveromyces marxianus* YAS through overexpression of BAX, CASP 3, CASP 8 and CASP 9 on human colon cancer cell lines, *Int. J. Biol. Biomol. Agric. Food Biotechnol. Eng.* (2016) 10.
- [92] R.E. Ley, Obesity and the human microbiome, *Curr. Opin. Gastroenterol.* 26 (2010) 5–11.
- [93] L. Zhao, The gut microbiota and obesity: from correlation to causality, *Nat. Rev. Microbiol.* 11 (2013) 639–647.
- [94] P.J. Turnbaugh, R.E. Ley, M.A. Mahowald, V. Magrini, E.R. Mardis, J.I. Gordon, An obesity-associated gut microbiome with increased capacity for energy harvest, *Nature* 444 (2006) 1027–1131.
- [95] H. Zhang, J.K. DiBaise, A. Zuccolo, D. Kudrna, M. Braidotti, Y. Yu, et al., Human gut microbiota in obesity and after gastric bypass, *Proc. Natl. Acad. Sci. U. S. A.* 106 (2009) 2365–2370.
- [96] M.F. Gregor, G.S. Hotamisligil, Inflammatory mechanisms in obesity, *Annu. Rev. Immunol.* 29 (2011) 415–445.

- [97] P.D. Cani, S. Possemiers, T. Van de Wiele, Y. Guiot, A. Everard, O. Rottier, et al., Changes in gut microbiota control inflammation in obese mice through a mechanism involving GLP-2-driven improvement of gut permeability, *Gut* 58 (2009) 1091–1103.
- [98] F. Bäckhed, J.K. Manchester, C.F. Semenkovich, J.I. Gordon, Mechanisms underlying the resistance to diet-induced obesity in germ-free mice, *Proc. Natl. Acad. Sci. U. S. A.* 104 (2007) 979–984.
- [99] C.K. Fleissner, N. Huebel, M.M.A. El-Bary, G. Loh, S. Klaus, M. Blaut, Absence of intestinal microbiota does not protect mice from diet-induced obesity, *Br. J. Nutr.* 104 (2010) 919–929.
- [100] F. Bäckhed, H. Ding, T. Wang, L.V. Hooper, G.Y. Koh, A. Nagy, et al., The gut microbiota as an environmental factor that regulates fat storage, *Proc. Natl. Acad. Sci. U. S. A.* 101 (2004) 15718–15723.
- [101] B. Fontaine-Bisson, F. Renström, O. Rolandsson, F. Payne, G. Hallmans, I. Barroso, et al., Evaluating the discriminative power of multi-trait genetic risk scores for type 2 diabetes in a northern Swedish population, *Diabetologia* 53 (2010) 2155–2162.
- [102] K. Forslund, F. Hildebrand, T. Nielsen, G. Falony, E. Le Chatelier, S. Sunagawa, et al., Disentangling type 2 diabetes and metformin treatment signatures in the human gut microbiota, *Nature* 528 (2015) 262–266.
- [103] J. Xu, F. Lian, L. Zhao, Y. Zhao, X. Chen, X. Zhang, et al., Structural modulation of gut microbiota during alleviation of type 2 diabetes with a Chinese herbal formula, *ISME J.* 9 (2015) 552–562.
- [104] S.E. Epstein, J. Zhu, M.S. Burnett, Y.F. Zhou, G. Vercellotti, Hajjar D. Infection, Atherosclerosis potential roles of pathogen burden and molecular mimicry, *Arterioscler. Thromb. Vasc. Biol.* 20 (2000) 1417–1420.
- [105] K.J. Mattila, P.J. Pussinen, S. Paju, Dental infections and cardiovascular diseases: a review, *J. Periodontol.* 76 (2005) 2085–2088.
- [106] S. Jerwood, J. Cohen, Unexpected antimicrobial effect of statins, *J. Antimicrob. Chemother.* 61 (2008) 362–364.
- [107] O. Koren, A. Spor, J. Felin, F. Fåk, J. Stombaugh, V. Tremaroli, et al., Human oral, gut, and plaque microbiota in patients with atherosclerosis, *Proc. Natl. Acad. Sci. U. S. A.* 108 (2011) 4592–4598.
- [108] S.J. Ott, N.E. El Mokhtari, M. Musfeldt, S. Hellmig, S. Freitag, A. Rehman, et al., Detection of diverse bacterial signatures in atherosclerotic lesions of patients with coronary heart disease, *Circulation* 113 (2006) 929–937.
- [109] F.H. Karlsson, F. Fåk, I. Nookaew, V. Tremaroli, B. Fagerberg, D. Petranovic, et al., Symptomatic atherosclerosis is associated with an altered gut metagenome, *Nat. Commun.* 3 (2012) 1245.
- [110] A. Toulouse, A.M. Sullivan, Progress in Parkinson's disease—where do we stand, *Prog. Neurobiol.* 85 (2008) 376–392.
- [111] J. Hardy, P. Lewis, T. Revesz, A. Lees, C. Paisan-Ruiz, The genetics of Parkinson's syndromes: a critical review, *Curr. Opin. Genet. Dev.* 19 (2009) 254–265.
- [112] E.A. Mayer, R. Knight, S.K. Mazmanian, J.F. Cryan, K. Tillisch, Gut microbes and the brain: paradigm shift in neuroscience, *J. Neurosci.* 34 (2014) 15490–15496.
- [113] J.F. Cryan, T.G. Dinan, Mind-altering microorganisms: the impact of the gut microbiota on brain and behaviour, *Nat. Rev. Neurosci.* 13 (2012) 701–712.
- [114] A. Keshavarzian, S.J. Green, P.A. Engen, R.M. Voigt, A. Naqib, C.B. Forsyth, et al., Colonic bacterial composition in Parkinson's disease, *Mov. Disord.* 30 (2015) 1351–1360.
- [115] E.A. Mayer, K. Tillisch, The brain-gut axis in abdominal pain syndromes, *Annu. Rev. Med.* 62 (2011).
- [116] M.H. McLean, D. Dieguez, L.M. Miller, H.A. Young, Does the microbiota play a role in the pathogenesis of autoimmune diseases? *Gut* 64 (2014), <http://dx.doi.org/10.1136/gutjnl-2014-308514>.
- [117] S. van Hemert, A.C. Breedveld, J. Rovers, J. Vermeiden, B. Witteman, M.G. Smits, et al., Migraine associated with gastrointestinal disorders: review of the literature and clinical implications, *Front. Neurol.* 5 (2013) 241–.
- [118] S. O'Mahony, V. Felice, K. Nally, H. Savignac, M. Claesson, P. Scully, et al., Disturbance of the gut microbiota in early-life selectively affects visceral pain in adulthood without impacting cognitive or anxiety-related behaviors in male rats, *Neuroscience* 277 (2014) 885–901.
- [119] S. O'Mahony, G. Clarke, Y. Borre, T. Dinan, J. Cryan, Serotonin: tryptophan metabolism and the brain-gut-microbiome axis, *Behav. Brain Res.* 277 (2015) 32–48.
- [120] E.A. Mayer, T. Savidge, R.J. Shulman, Brain?gut microbiome interactions and functional bowel disorders, *Gastroenterology* 146 (2014) 1500–1512.