European Review for Medical and Pharmacological Sciences 2016; 20: 4742-4749

The role of diet on gut microbiota composition

S. BIBBÒ[1,2], G. IANIRO[1], V. GIORGIO[3], F. SCALDAFERRI[1], L. MASUCCI[4], A. GASBARRINI[1], G. CAMMAROTA[1]

[1]Internal Medicine, Gastroenterology and Liver Unit, Catholic University of the Sacred Heart, School of Medicine, A. Gemelli Foundation, Rome, Italy
[2]Department of Clinical and Experimental Medicine, University of Sassari, Italy
[3]Division of Pediatrics, Catholic University of the Sacred Heart, School of Medicine A. Gemelli Foundation, Rome, Italy
[4]Institute of Microbiology, Catholic University of the Sacred Heart, A. Gemelli Foundation, School of Medicine, Rome, Italy

Abstract. – Gut microbiota is characterized by an inter-individual variability due to genetic and environmental factors. Among the environmental ones, dietary habits play a key role in the modulation of gut microbiota composition. There are main differences between the intestinal microbiota of subjects fed with prevalent Western diet and that of subjects with a diet rich in fibers. Specific changes in the composition of gut microbiota have been demonstrated among subjects according to a different dietary intake. A particular diet may promote the growth of specific bacterial strains, driving hosts to a consequent alteration of fermentative metabolism, with a direct effect on intestinal pH, which can be responsible for the development of a pathogenic flora. Moreover, a high-fat diet can promote the development of a pro-inflammatory gut microbiota, with a consequent increase of intestinal permeability and, consequently, of circulating levels of lipopolysaccharides.

In this review, we discuss the direct role of the diet in the composition of gut microbiota and about the possible clinical consequences.

Key Words:
Gut microbiota, Diet, Inflammation, Lipopolysaccharide, Fiber, High-fat.

Introduction

Our organism is colonized by an enormous number of micro-organisms, both on its surface and inside. They amount for more than 1 kg of weight, and outnumber human eukaryotic cells at least ten times. The majority of them live in our gut, constituting the so-called gut microbiota[1]. As gut microbiota and human beings are in a symbiotic relationship, the idea of a combined "super-organism" has been recently developed[2].

In health, gut microbiota plays a relevant role within our body, mainly being involved in the development and growth of immunity and in the regulation of several fundamental metabolic pathways[3-5].

Quantitative and/or qualitative alterations of gut microbiota bring to the impairment of this homeostasis, leading to the development of several gut microbiota-related diseases[6,7], such as functional gastrointestinal diseases[8], intestinal infectious diseases[9,10], inflammatory bowel disease[11,12], liver diseases[13,14], gastrointestinal malignancies[15], obesity and metabolic syndrome[16], diabetes mellitus[17], allergic diseases[18], autism[19], and others.

Since a large part of microorganisms, in particular, anaerobes, is not cultivable through conventional microbiology techniques, our understanding of gut microbiota is substantially limited. However, the development of culture-independent tools, based on metagenomics technologies, has led us to take a step forward in the assessment of gut microbiota composition[20].

Currently, four major microbial phyla are known to represent over 90% of the bacterial component of gut microbiota: *Firmicutes, Bacteroides, Proteobacteria* and *Actinobacteria*. The majority of "good" bacteria harbouring the human gut microbiota are represented by *Firmicutes* and *Cytophaga-Flavobacterium-Bacteroides* (CFB). *Firmicutes* are sub-grouped in *Clostridium coccoides* (Clostridium cluster XIVa) and *Clostridium leptum* (Clostridium cluster IV); whereas CFB group is represented mainly by *Bacteroides phyla* with a great number of *Prevotella* and *Porphyromonas*[10,21].

Moreover, our gut microbiota includes viruses, especially phages, Eukarya, as Fungi, Blastocystis, Amoebozoa, and Archaea[22,23,24].

Corresponding Author: Stefano Bibbò, MD; e-mail: s.bibbo@gmail.com

Gut microbiota has been classified into three main enterotypes, each one owning specific metabolic features[25]. Each enterotype is characterized by the relative abundance of one of the following genera: *Bacteroides* (more represented in enterotype 1), *Prevotella* (more abundant in enterotype 2), *Ruminococcus* (prevalent in enterotype 3). Prevalence of a specific enterotype can depend on long-term dietary habits, indeed high-fat and protein diet enhances the growth of enterotypes 1 and 3, while a diet rich in carbohydrates supports the raise of enterotype 2[26]. Recent findings suggest that gut microbiota composition is influenced also by short-term dietary changes[27].

Both genetic and environmental factors are involved in influencing the inter-individual diversity of gut microbiota. Among environmental ones, the interest of the scientific community in dietary factors has progressively increased, and the role of diet on the composition of gut microbiota has been particularly emphasized over the last years[28-31].

Relationship Between Diet and Gut Microbiota

Diet is known to have a strong influence on the composition of intestinal microbiota[31]. To confirm this hypothesis, some researchers sequenced oral microbiota from skeleton teeth of people who lived over the various eras. They showed that the most significant changes in human gut microbiota had occurred during two socio-dietary breakthroughs over the human history: the passage from the hunter-gatherer Paleolithic era to the farming Neolithic era (10000 years ago), with a diet rich in carbohydrates, and the beginning of the industrialized period, characterized by processed flour and sugar diet (about two centuries ago)[32,33].

Further studies identified also differences in gut microbiota composition among different populations of our planet, probably due to variability in both diet and genetics of each population.

De Filippo et al[34] have compared the gut microbiota of children from rural Africa (Burkina Faso) with that of Italian children living in urban areas showing that these two populations have radically different diets; in particular, open children have a lower dietary intake of fibers. The bacterial profiles of the two groups of children clustered separately: microbiota of the African children is dominated by Bacteroidetes, whereas among European children there is a prevalence of *Enterobacteriaceae* and a decrease in *Bacteroides*.

Large variations in gut microbiota among Americans, Europeans and Africans have also been documented in other studies. Gut microbiome of Africans clustered with that of South American people, correlating with large consumption of plant-based polysaccharides, but were different from North Americans (which have mainly a low-fiber diet). Carbohydrates intake from the diet could, therefore, contribute to the large variation observed in gut microbiota composition[35]. Indeed, a high-fiber diet seems to be positively correlated with bacterial richness. Therefore, permanent changes in gut microbiota composition might be achieved through dietary modifications[26,36].

While Western diet, typically constituted by high consumption of red meat, animal fat, high sugar and low fiber food[37], was therefore associated with an increased number of *Bacteroides phyla* (mainly mucin-degrading bacteria) and also *Ruminococcus*[38].

Specific changes in the gut microbiota have been associated with long-term or short-term dietary modifications. Wu and colleagues found that the microbiota composition is strongly associated with long-term dietary habits. Prevalence of *Bacteroides* and *Actinobacteria* is positively associated with high-fat diet, but is negatively associated with fiber intake, whereas *Firmicutes* and *Proteobacteria* show the opposite association. Bacteroidetes-predominant enterotype is strictly associated with animal protein and saturated fats, suggesting its prevalence in Western countries. In contrast, *Prevotella*-prevailing enterotype is associated with high consumption of carbohydrates and simple sugars, indicating a correlation with a carbohydrate based diet more typical of agrarian societies and vegetarians[26].

Also, a short-term dietary alterations can modify the microbial communities of our body. An animal-based diet increased the abundance of bile-tolerant microorganisms (such as *Alistipes*, *Bilophila* and *Bacteroides*) and decreased the levels of *Firmicutes* metabolizing dietary plant polysaccharides (*Roseburia*, *Eubacterium rectale* and *Ruminococcus bromii*). Such data confirm the existing differences between gut microbiota of vegetarians and mainly carnivorous subjects, that are fundamental respectively for carbohydrate and protein fermentation[27].

High-fiber diet and gut microbiota

Dietary fibers are divided into complex carbohydrates (digestible and non-digestible) and oligosaccharides. They exert a strong influence

Table I. Effect of carbohydrates on gut microbiota composition.

Resistant starch 2	↑ Ruminococcus spp, Eubacterium rectale, Bifidobacterium adolescentis
Resistant starch 3	↑ Eubacterium rectale, Roseburia spp, Ruminococcus bromii
Resistant starch 4	↑ Parabacteroides diastasonis ↓ Eubacterium rectale, Ruminococcus bromii
High soluble fiber diet	↑ Bacteroides spp., C. leptum group, and E. rectale
Complex carbohydrates	↑ Bifidobacteria spp, Prevotella spp
Low fiber diet	↓ Roseburia spp, Eubacterium rectale

on the composition of the gut microbiota and consequently on the gut fermentative metabolism.

Complex carbohydrates

A fraction of normal human dietary intake remains undigested in the small intestine and passes through to the large intestine to be eliminated. Non-digestible components include plant cell wall polysaccharides (such as cellulose and pectin) and certain storage polysaccharides (such as inulin and oligosaccharides). Dietary starch incorporates a resistant component that is not fully digested in the small intestine[39,40]. There are four types of resistant starch (RS1 to RS4) consumed with diet[29]. Resistance features of dietary starch are respectively the protection from plant cell wall polymers (type 1), granular structure (type 2), retro-gradation resulting from heating and cooling (type 3) or chemical cross-linking (type 4)[41].

Several studies have analyzed the role of different types of resistant starch in gut microbiota regulation. Leitch et al[42] showed that subjects fed with resistant starch type 2 (RS2) from high amylose maize showed an increased abundance of *Ruminococcus spp.* and *Eubacterium rectale*, while consumption of RS 3 promoted the growth of *Eubacterium rectale, Roseburia spp.* and *Ruminococcus bromii*[42].

Additionally, RS2 have been shown to promote an enrichment of *Bifidobacterium adolescentis*, *Eubacterium rectale*, and *Ruminococcus bromii.* These last two species are increased during RS3 consumption. Moreover, RS4 is positively correlated with *Parabacteroides distasonis* abundance and negatively correlated with *Eubacterium rectale* and *Ruminococcus bromii* prevalence. Strikingly, RS4 also leads to phylum level alterations, decreasing the proportion of *Firmicutes* while increasing *Bacteroides* and Actinobacteria[43]. Walker et al[44] confirmed that *Firmicutes* bacteria related to *Ruminococcus bromii* and *Eubacterium rectale* are commonly stimulated by the RS diet.

Furthermore, the consumption of high quantities of soluble diet leads to increase in *Bacteroides spp.*, *Clostridium leptum* group bacteria, and Eubacterium rectale group[45]. Soluble fibers are indeed associated with an increased proportion of butyrate-producing bacteria, that mainly belong to the *Clostridium leptum* and *Eubacterium rectale* groups[46]. Moreover, complex carbohydrates also increase levels of beneficial bacteria, in particular, *Bifidobacteria spp.*, such as *B. longum*, *B. breve* and *B. thetaiotaomicron*[47]. Finally, *Prevotella spp.* are the most represented bacteria in vegetarian subjects[48].

On the other hand, a decrease in total carbohydrate dietary content leads to a significant decrease in the proportion of the *Roseburia/E. rectale* group (Table I)[49].

Oligosaccharides

Not only complex carbohydrates, but also oligosaccharides (such as fructans, inulin, fructo-oligosaccharides (FOSs), Galacto-oligosaccharides (GOS) and Arabinoxylan-oligosaccharides) have shown a role in modifying gut microbiota. Inulin and FOSs promote the growth of *Bifidobacterium spp* and, *Lactobacillus spp.*, whereas fructan supplementation decreases levels of *Bacteroides spp* and *Clostridium spp.*[50]. Furthermore, fructans can promote the growth of beneficial butyrate-producing bacteria, such as Faecalibacterium prausnitzii[51,52].

Galacto-oligosaccharides (GOS) supplementation can stimulate the growth of *Bifidobacteria spp* (especially *B. adolescentis* and *B. catenulatum*) and also increase the *Faecalibacterium prausnitzii* population, but with inter-individual variability[53,54]. Arabinoxylan-oligosaccharides display a similar behavior, and additionally increase total bacterial population (Table II)[55].

High-fat diet and gut microbiota

The role of fatty acids in the regulation of gut microbiota has been extensively assessed. Dietary fatty acids are grouped into three main categories: satura-

Table II. Effect of oligosaccharides on gut microbiota composition.

Fructo-oligosaccharides	↑ Bifidobacterium spp, Lactobacillus spp
Inulin	↑ Bifidobacterium spp, Lactobacillus spp
Fructans	↓ Bacteroides spp, Clostridium spp
Galacto-oligosaccharides	↑ Bifidobacterium spp, F. prausnitzii
Arabinoxylan-oligosaccharides	↑ Bifidobacterium spp

ted (SFA), monounsaturated (MUFA), polyunsaturated (PUFA). Essential PUFAs are represented by two important families[56]: ω-6 and ω-3.

Several papers explain the role of specific fatty acids. A high-fat diet rich in safflower oil (that contains ω-6 PUFA) reduces the populations of Bacteroides while enriching the populations of Firmicutes, Actinobacteria and Proteobacteria[57].

In vitro studies have assessed the effect of PUFAs on the growth and adhesion of different Lactobacillus strains (*L. rhamnosus* GG, *L. casei Shirota* and *L. delbrueckii* ssp *bulgaricus)*, with different results depending on the strain. High concentrations of PUFA inhibit both adhesion to mucus and growth of all tested bacterial strains, whereas small quantities of gamma-linolenic acid and arachidonic acid promote growth and mucus adhesion of *L. casei Shirota*[58,59].

In humans, high intake of MUFA was associated with lower levels of *Bifidobacteria spp* and slightly higher numbers of *Bacteroides spp.* In the same study higher ω-6 PUFA intake was associated with a decreased number of *Bifidobacteria*[45].

Some studies have shown the effect of high-fat dietary pattern. For instance, a regular consumption of red meat is responsible of a major concentration of Bacteroides[60]. Moreover, a diet rich in saturated fats (for example milk) has shown ability in triggering the growth of delta-Proteobacteria, specifically *Bilophila wadsworthia*[61]. Interestingly, a high-fat diet generates dysbiosis, leading to a significant reduction in numbers of *Roseburia* species (Table III)[62].

Metabolic effects

The effect of dietary induced changes of gut microbiota on local and systemic inflammation has also been extensively investigated. Intestinal barrier plays an important role in the regulation of the immune system, in particular through gut microbiota[6,7]. Gut microbiota can alter the function and feedbacks of intestinal immune cells, by regulating systemic and mucosal immunity[63]. For this reason, there is a growing interest for factors, such as diet, that can modulate gut microbiota itself[56,64].

High fiber diet alters fermentative metabolites and intestinal pH. Colonic microbiota is able to metabolize complex carbohydrates and sugars into short-chain fatty acids (SCFAs), such as acetate, butyrate and propionate. Such metabolites play a role in regulating intestinal pH[30].

For instance, in vegetarian subjects, the high amounts of fiber result in an increase of SCFAs production by microbes, which lower the local pH[65]. Little variation of acid concentrations may exert important consequences. A one-unit decrease in pH (from 6.5 to 5.5) has been shown to have a profound selective effect on the colonic microbial population, with a prevalent decrease of Bacteroides spp. and a growth of butyrate-producing gram-positive bacteria[66].

The decrease of pH caused by high concentration of SCFAs prevents the growth of potentially pathogenic bacteria, such as *E. coli* and other members of the *Enterobacteriaceae*[65,67]. Moreover, SCFAs

Table III. Effect of high-fat diet on gut microbiota composition.

Safflower oil (ω-6 PUFA)	↑ Firmicutes, Actinobacteria, Proteabacteria
	↓ Bacteroides
PUFA	↓ Lactobacillus spp
ω -6 PUFA	↓ Bifidobacteria spp
↓PUFA	↑ L. casei Shirota
MUFA	↓ Bifidobacteria spp
High-fat diet	↑ delta-proteabacteria spp, Bilophila wadsworthia
	↓ Roseburia spp

production can be a potential modulator of intestinal flora. Several gut bacteria, such as some *Firmicutes spp*, especially those belonging to *Clostridium cluster* XIVa, are tolerant of lower, while *Bacteroides* spp. and Bifidobacterium spp are not[63,66].

Western diet was considered responsible of the intestinal dysbiosis that triggers local inflammation, causing an increase of intestinal permeability[37]. It is known that certain types of intestinal flora may promote inflammation. The exact mechanism is, however, not completely understood. Besides, metabolic adaptation to high-fat diet is associated to a change in gut microbiota composition[68,69].

It was observed that high fat diet induces the proliferation of certain gram-negative bacteria, such as Enterobacteriaceae, which can ultimately result in increased intestinal lipopolysaccharide (LPS)[70]. To confirm this Pendyala et al[71] reported that only 1 month of western diet is responsible of an important increase of LPS plasma levels.

Furthermore, increased gut permeability is associated with a decrease in *Bifidobacteria spp*, bacteria that are known to reduce LPS levels and also improve gut barrier function. Interestingly, prebiotic treatment with non-digestible carbohydrates increases *Bifidobacteria*, reduces intestinal permeability, LPS concentrations, and metabolic endotoxaemia[72].

In a mouse model, consumption of a high-fat diet increased the incidence of colonic inflammation; this effect seems to be induced by the secretion of bile acid, in particular taurine, promoted by fat food. Such phenomenon stimulates the growth of sulphite-reducing pathobionts such as Bilophila wadsworthia, whose production of H_2S is thought to inflame intestinal mucosa. *Bilophila wadsworthia* is promoted by a high-fat diet also in human beings[27,61]. Moreover, high-fat diet causes low-grade inflammation in the gut, leading to increased levels of plasma markers of inflammation, and higher levels of circulating LPS[73].

A decreased numbers of *Bifidobacteria* was associated with the higher ω-6 PUFA intake[45]. Interestingly, high ω-6 PUFA intake decreases certain immune functions, such as T-helper Th1 and Th2 responses, adhesion molecule expression and proinflammatory cytokines[74]. Moreover, high-protein diet stimulates the activity of bacterial enzymes such as B-glucorinidase, azoreductase and nitroreductase, which produce toxic metabolites that trigger inflammatory response[31].

Consequently, the Western diet can therefore create the favorable conditions for chronic endotoxiemia, defined as an excess of circulating bacterial wall LPS, through the impairment in gastrointestinal barrier function and the changes of the microbiota. Endotoxemia is associated with systemic inflammation and with the metabolic syndrome[71,75].

Conclusions

In this review, we analyzed how dietary factors can modify the gut microbiota. Recent discoveries have allowed us to set aside the idea that only individual genetics play a role in determining the composition of the intestinal flora. It is evident how the food choice of every individual, both because of survival needs and taste preference, causes a substantial and significant variability in gut microbiota. As increasing evidence is showing us, diet can be definitely included, as it is for antibiotics, among the microbiota modulators, with a two-faced behavior toward gastrointestinal disorders[76,77].

We have briefly discussed how a diet rich in fats may favor an "inflammatory" flora. Diet rich in fats and low in fibers, typical of Western Countries, is rapidly spreading around the world. Similarly, inflammatory diseases are increasing in prevalence even in areas where were less common until a few years ago. Between these two observations maybe there is a link, which could be represented by the diet. It is still too early to comprise whether this is only a suggestion or if behind this observation there is a precise pathophysiological mechanism. For this reason, further studies are needed to understand the role of the intestinal barrier, and in particular of gut microbiota, in the development of systemic and local immune response. Full understanding of this issue will provide the medical community with new therapeutic targets for gastrointestinal and extraintestinal disorders.

Conflicts of interest

The authors declare no conflicts of interest.

References

1) Rajilic-Stojanovic M, de Vos WM. The first 1000 cultured species of the human gastrointestinal microbiota. FEMS Microbiol Rev 2014; 38: 996-1047.

2) Turnbaugh PJ, Ley RE, Hamady M, Fraser-Liggett CM, Knight R, Gordon JI. The human microbiome project. Nature 2007; 449: 804-810.

3) Purchiaroni F, Tortora A, Gabrielli M, Bertucci F, Gigante G, Ianiro G, Ojetti V, Scarpellini E, Gasbarrini A . The role of intestinal microbiota and the immune system. Eur Rev Med Pharmacol Sci 2013; 17: 323-333.

4) Sekirov I, Russell SL, Antunes LC, Finlay BB. Gut microbiota in health and disease. Physiol Rev 2010; 90: 859-904.

5) Rajilic-Stojanovic M. Function of the microbiota. Best Pract Res Clin Gastroenterol 2013; 27: 5-16.

6) Viggiano D, Ianiro G, Vanella G, Bibbo S, Bruno G, Simeone G, Mele G. Gut barrier in health and disease: focus on childhood. Eur Rev Med Pharmacol Sci 2015; 19: 1077-1085.

7) Lopetuso LR, Scaldaferri F, Bruno G, Petito V, Franceschi F, Gasbarrini A. The therapeutic management of gut barrier leaking: the emerging role for mucosal barrier protectors. Eur Rev Med Pharmacol Sci 2015; 19: 1068-1076.

8) Simren M, Barbara G, Flint HJ, Spiegel BM, Spiller RC, Vanner S, Verdu EF, Whorwell PJ, Zoetendal EG. Intestinal microbiota in functional bowel disorders: a Rome foundation report. Gut 2013; 62: 159-176.

9) DuPont AW, DuPont HL. The intestinal microbiota and chronic disorders of the gut. Nat Rev Gastroenterol Hepatol 2011; 8: 523-531.

10) Bibbo S, Lopetuso LR, Ianiro G, Di Rienzo T, Gasbarrini A, Cammarota G. Role of microbiota and innate immunity in recurrent Clostridium difficile infection. J Immunol Res 2014; 2014: 462740.

11) Manichanh C, Borruel N, Casellas F, Guarner F. The gut microbiota in IBD. Nat Rev Gastroenterol Hepatol 2012; 9: 599-608.

12) Cammarota G, Ianiro G, Cianci R, Bibbo S, Gasbarrini A, Curro D. The involvement of gut microbiota in inflammatory bowel disease pathogenesis: potential for therapy. Pharmacol Ther 2015; 149: 191-212.

13) Aron-Wisnewsky J, Gaborit B, Dutour A, Clement K. Gut microbiota and non-alcoholic fatty liver disease: new insights. Clin Microbiol Infect 2013; 19: 338-348.

14) Dhiman RK. Gut microbiota and hepatic encephalopathy. Metab Brain Dis 2013; 28: 321-326.

15) Zhu Q, Gao R, Wu W, Qin H. The role of gut microbiota in the pathogenesis of colorectal cancer. Tumour Biol 2013; 34: 1285-300.

16) D'Aversa F, Tortora A, Ianiro G, Ponziani FR, Annicchiarico BE, Gasbarrini A. Gut microbiota and metabolic syndrome. Intern Emerg Med 2013; 8: S11-15.

17) Bibbo S, Dore MP, Pes GM, Delitala G, Delitala AP. Is There a Role for Gut Microbiota in Type 1 Diabetes Pathogenesis? Ann Med 2016: 1-25.

18) Prince BT, Mandel MJ, Nadeau K, Singh AM. Gut Microbiome and the Development of Food Allergy and Allergic Disease. Pediatr Clin North Am 2015; 62: 1479-1492.

19) Li Q, Zhou JM. The microbiota-gut-brain axis and its potential therapeutic role in autism spectrum disorder. Neuroscience 2016; 324: 131-139.

20) Zoetendal EG, Rajilic-Stojanovic M, de Vos WM. High-throughput diversity and functionality analysis of the gastrointestinal tract microbiota. Gut 2008; 57: 1605-1615.

21) Cani PD. Metabolism in 2013: The gut microbiota manages host metabolism. Nat Rev Endocrinol 2014; 10: 74-76.

22) Ianiro G, Bruno G, Lopetuso L, Beghella Bartoli F, Laterza L, D'Aversa F, Gigante G, Cammarota G, Gasbarrini A. Role Of Yeasts In Healthy And Impaired Gut Microbiota: The Gut Mycome. Curr Pharm Des 2013; 20: 4565-4569.

23) Lozupone CA, Stombaugh JI, Gordon JI, Jansson JK, Knight R. Diversity, stability and resilience of the human gut microbiota. Nature 2012; 489: 220-230.

24) Columpsi P, Sacchi P, Zuccaro V, Cima S, Sarda C, Mariani M, Gori A, Bruno R. Beyond the gut bacterial microbiota: The gut virome. J Med Virol 2016; 88: 1467-1472.

25) Arumugam M, Raes J, Pelletier E, Le Paslier D, Yamada T, Mende DR, Fernandes GR, Tap J, Bruls T, Batto JM, Bertalan M, Borruel N, Casellas F, Fernandez L, Gautier L, Hansen T, Hattori M, Hayashi T, Kleerebezem M, Kurokawa K, Leclerc M, Levenez F, Manichanh C, Nielsen HB, Nielsen T, Pons N, Poulain J, Qin J, Sicheritz-Ponten T, Tims S, Torrents D, Ugarte E, Zoetendal EG, Wang J, Guarner F, Pedersen O, de Vos WM, Brunak S, Doré J; MetaHIT Consortium, Antolín M, Artiguenave F, Blottiere HM, Almeida M, Brechot C, Cara C, Chervaux C, Cultrone A, Delorme C, Denariaz G, Dervyn R, Foerstner KU, Friss C, van de Guchte M, Guedon E, Haimet F, Huber W, van Hylckama-Vlieg J, Jamet A, Juste C, Kaci G, Knol J, Lakhdari O, Layec S, Le Roux K, Maguin E, Mérieux A, Melo Minardi R, M'rini C, Muller J, Oozeer R, Parkhill J, Renault P, Rescigno M, Sanchez N, Sunagawa S, Torrejon A, Turner K, Vandemeulebrouck G, Varela E, Winogradsky Y, Zeller G, Weissenbach J, Ehrlich SD, Bork P. Enterotypes of the human gut microbiome. Nature 2011; 473:174-180.

26) Wu GD, Chen J, Hoffmann C, Bittinger K, Chen YY, Keilbaugh SA, Bewtra M, Knights D, Walters WA, Knight R, Sinha R, Gilroy E, Gupta K, Baldassano R, Nessel L, Li H, Bushman FD, Lewis JD. Linking long-term dietary patterns with gut microbial enterotypes. Science 2011; 334: 105-108.

27) David LA, Maurice CF, Carmody RN, Gootenberg DB, Button JE, Wolfe BE, Ling AV, Devlin AS, Varma Y, Fischbach MA, Biddinger SB, Dutton RJ, Turnbaugh PJ. Diet rapidly and reproducibly alters the human gut microbiome. Nature 2014; 505: 559-563.

28) Claesson MJ, Jeffery IB, Conde S, Power SE, O'Connor EM, Cusack S, Harris HM, Coakley M, Lakshminarayanan B, O'Sullivan O, Fitzgerald GF, Deane J, O'Connor M, Harnedy N, O'Connor K, O'Mahony D, van Sinderen D, Wallace M, Brennan L, Stanton C, Marchesi JR, Fitzgerald AP, Shanahan F, Hill C, Ross RP, O'Toole PW. Gut microbiota composition correlates with diet and health in the elderly. Nature 2012; 488: 178-184.

29) Scott KP, Gratz SW, Sheridan PO, Flint HJ, Duncan SH. The influence of diet on the gut microbiota. Pharmacol Res 2013; 69: 52-60.

30) Chassard C, Lacroix C. Carbohydrates and the human gut microbiota. Curr Opin Clin Nutr Metab Care 2013; 16: 453-460.

31) Brown K, DeCoffe D, Molcan E, Gibson DL. Diet-induced dysbiosis of the intestinal microbiota and the effects on immunity and disease. Nutrients 2012; 4: 1095-1119.

32) Chan YK, Estaki M, Gibson DL. Clinical consequences of diet-induced dysbiosis. Ann Nutr Metab 2013; 63: 28-40.

33) Adler CJ, Dobney K, Weyrich LS, Kaidonis J, Walker AW, Haak W, Bradshaw CJ, Townsend G, Sołtysiak A, Alt KW, Parkhill J, Cooper A. Sequencing ancient calcified dental plaque shows changes in oral microbiota with dietary shifts of the Neolithic and Industrial revolutions. Nat Genet 2013; 45: 450-455.

34) De Filippo C, Cavalieri D, Di Paola M, Ramazzotti M, Poullet JB, Massart S, Collini S, Pieraccini G, Lionetti P. 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 2010; 107: 14691-14696.

35) Yatsunenko T, Rey FE, Manary MJ, Trehan I, Dominguez-Bello MG, Contreras M, Magris M, Hidalgo G, Baldassano RN, Anokhin AP, Heath AC, Warner B, Reeder J, Kuczynski J, Caporaso JG, Lozupone CA, Lauber C, Clemente JC, Knights D, Knight R, Gordon JI. Human gut microbiome viewed across age and geography. Nature 2012; 486:222-227.

36) Cotillard A, Kennedy SP, Kong LC, Prifti E, Pons N, Le Chatelier E, Almeida M, Quinquis B, Levenez F, Galleron N, Gougis S, Rizkalla S, Batto JM, Renault P; ANR MicroObes consortium, Doré J, Zucker JD, Clément K, Ehrlich SD. Dietary intervention impact on gut microbial gene richness. Nature 2013; 500: 585-588.

37) Hold GL. Western lifestyle: a 'master' manipulator of the intestinal microbiota? Gut 2014; 63:5-6.

38) Mukhopadhya I, Hansen R, El-Omar EM, Hold GL. IBD-what role do Proteobacteria play? Nat Rev Gastroenterol Hepatol 2012; 9: 219-230.

39) Bird AR, Brown IL, Topping DL. Starches, resistant starches, the gut microflora and human health. Curr Issues Intest Microbiol 2000; 1: 25-37.

40) Flint HJ. The impact of nutrition on the human microbiome. Nutr Rev 2012; 70: S10-13.

41) Flint HJ, Scott KP, Duncan SH, Louis P, Forano E. Microbial degradation of complex carbohydrates in the gut. Gut Microbes 2012; 3: 289-306.

42) Leitch EC, Walker AW, Duncan SH, Holtrop G, Flint HJ. Selective colonization of insoluble substrates by human faecal bacteria. Environ Microbiol 2007; 9: 667-679.

43) Martinez I, Kim J, Duffy PR, Schlegel VL, Walter J. Resistant starches types 2 and 4 have differential effects on the composition of the fecal microbiota in human subjects. PLoS One 2010; 5: e15046.

44) Walker AW, Ince J, Duncan SH, Webster LM, Holtrop G, Ze X, Brown D, Stares MD, Scott P, Bergerat A, Louis P, McIntosh F, Johnstone AM, Lobley GE, Parkhill J, Flint HJ. Dominant and diet-responsive groups of bacteria within the human colonic microbiota. ISME J 2011; 5: 220-230.

45) Simoes CD, Maukonen J, Kaprio J, Rissanen A, Pietilainen KH, Saarela M. Habitual dietary intake is associated with stool microbiota composition in monozygotic twins. J Nutr 2013; 143: 417-423.

46) Louis P, Scott KP, Duncan SH, Flint HJ. Understanding the effects of diet on bacterial metabolism in the large intestine. J Appl Microbiol 2007; 102: 1197-1208.

47) Pokusaeva K, Fitzgerald GF, van Sinderen D. Carbohydrate metabolism in Bifidobacteria. Genes Nutr 2011; 6: 285-306.

48) Liszt K, Zwielehner J, Handschur M, Hippe B, Thaler R, Haslberger AG. Characterization of bacteria, clostridia and Bacteroides in faeces of vegetarians using qPCR and PCR-DGGE fingerprinting. Ann Nutr Metab 2009; 54: 253-257.

49) Duncan SH, Belenguer A, Holtrop G, Johnstone AM, Flint HJ, Lobley GE. Reduced dietary intake of carbohydrates by obese subjects results in decreased concentrations of butyrate and butyrate-producing bacteria in feces. Appl Environ Microbiol 2007; 73: 1073-1078.

50) Scott KP, Martin JC, Chassard C, Clerget M, Potrykus J, Campbell G, Mayer CD, Young P, Rucklidge G, Ramsay AG, Flint HJ. Substrate-driven gene expression in Roseburia inulinivorans: importance of inducible enzymes in the utilization of inulin and starch. Proc Natl Acad Sci U S A 2011; 108: 4672-4679.

51) Dewulf EM, Cani PD, Claus SP, Fuentes S, Puylaert PG, Neyrinck AM, Bindels LB, de Vos WM, Gibson GR, Thissen JP, Delzenne NM. Insight into the prebiotic concept: lessons from an exploratory, double blind intervention study with inulin-type fructans in obese women. Gut 2013; 62: 1112-1121.

52) Ramirez-Farias C, Slezak K, Fuller Z, Duncan A, Holtrop G, Louis P. Effect of inulin on the human gut microbiota: stimulation of Bifidobacterium adolescentis and Faecalibacterium prausnitzii. Br J Nutr 2009; 101: 541-550.

53) Davis LM, Martinez I, Walter J, Goin C, Hutkins RW. Barcoded pyrosequencing reveals that consumption of galactooligosaccharides results in a highly specific bifidogenic response in humans. PLoS One 2011; 6: e25200.

54) Walton GE, van den Heuvel EG, Kosters MH, Rastall RA, Tuohy KM, Gibson GR. A randomised crossover study investigating the effects of galacto-oligosaccharides on the faecal microbiota in men and women over 50 years of age. Br J Nutr. 2012; 107: 1466-1475.

55) Walton GE, Lu C, Trogh I, Arnaut F, Gibson GR. A randomised, double-blind, placebo controlled cross-over study to determine the gastrointestinal effects of consumption of arabinoxylan-oligosaccharides enriched bread in healthy volunteers. Nutr J 2012; 11: 36.

56) Huang EY, Devkota S, Moscoso D, Chang EB, Leone VA. The role of diet in triggering human inflamma-

tory disorders in the modern age. Microbes Infect 2013; 15: 765-774.

57) Hildebrandt MA, Hoffmann C, Sherrill-Mix SA, Keilbaugh SA, Hamady M, Chen YY, Knight R, Ahima RS, Bushman F, Wu GD. High-fat diet determines the composition of the murine gut microbiome independently of obesity. Gastroenterology 2009; 137: 1716-1724.

58) Kankaanpaa P, Yang B, Kallio H, Isolauri E, Salminen S. Effects of polyunsaturated fatty acids in growth medium on lipid composition and on physicochemical surface properties of lactobacilli. Appl Environ Microbiol 2004; 70: 129-136.

59) Kankaanpaa PE, Salminen SJ, Isolauri E, Lee YK. The influence of polyunsaturated fatty acids on probiotic growth and adhesion. FEMS Microbiol Lett 2001; 194: 149-153.

60) N IJ, Derrien M, van Doorn GM, Rijnierse A, van den Bogert B, Muller M, Dekker J, Kleerebezem M, van der Meer R. Dietary heme alters microbiota and mucosa of mouse colon without functional changes in host-microbe cross-talk. PLoS One 2012; 7: e49868.

61) Devkota S, Wang Y, Musch MW, Leone V, Fehlner-Peach H, Nadimpalli A, Antonopoulos DA, Jabri B, Chang EB. Dietary-fat-induced taurocholic acid promotes pathobiont expansion and colitis in Il10-/- mice. Nature 2012; 487: 104-108.

62) Neyrinck AM, Possemiers S, Druart C, Van de Wiele T, De Backer F, Cani PD, Larondelle Y, Delzenne NM. Prebiotic effects of wheat arabinoxylan related to the increase in bifidobacteria, Roseburia and Bacteroides/Prevotella in diet-induced obese mice. PLoS One 2011; 6: e20944.

63) Jeffery IB, O'Toole PW. Diet-microbiota interactions and their implications for healthy living. Nutrients 2013; 5: 234-252.

64) Maslowski KM, Mackay CR. Diet, gut microbiota and immune responses. Nat Immunol 2011; 12: 5-9.

65) Zimmer J, Lange B, Frick JS, Sauer H, Zimmermann K, Schwiertz A, Rusch K, Klosterhalfen S, Enck P. A vegan or vegetarian diet substantially alters the human colonic faecal microbiota. Eur J Clin Nutr 2012; 66: 53-60.

66) Duncan SH, Louis P, Thomson JM, Flint HJ. The role of pH in determining the species composition of the human colonic microbiota. Environ Microbiol 2009; 11: 2112-2122.

67) Ghosh S, Dai C, Brown K, Rajendiran E, Makarenko S, Baker J, Ma C, Halder S, Montero M, Ionescu VA, Klegeris A, Vallance BA, Gibson DL. Colonic microbiota alters host susceptibility to infectious colitis by modulating inflammation, redox status, and ion transporter gene expression. Am J Physiol Gastrointest Liver Physiol 2011; 301: G39-49.

68) C YL. The Effect of High-Fat Diet-Induced Pathophysiological Changes in the Gut on Obesity: What Should be the Ideal Treatment? Clin Transl Gastroenterol 2013; 4: e39.

69) Serino M, Luche E, Gres S, Baylac A, Berge M, Cenac C, Waget A, Klopp P, Iacovoni J, Klopp C, Mariette J, Bouchez O, Lluch J, Ouarné F, Monsan P, Valet P, Roques C, Amar J, Bouloumié A, Théodorou V, Burcelin R. Metabolic adaptation to a high-fat diet is associated with a change in the gut microbiota. Gut 2012; 61: 543-553.

70) Kim KA, Gu W, Lee IA, Joh EH, Kim DH. High fat diet-induced gut microbiota exacerbates inflammation and obesity in mice via the TLR4 signaling pathway. PLoS One 2012; 7: e47713.

71) Pendyala S, Walker JM, Holt PR. A high-fat diet is associated with endotoxemia that originates from the gut. Gastroenterology 2012; 142: 1100-1101.

72) Duca FA, Sakar Y, Covasa M. The modulatory role of high fat feeding on gastrointestinal signals in obesity. J Nutr Biochem 2013; 24: 1663-1677.

73) Cani PD, Amar J, Iglesias MA, Poggi M, Knauf C, Bastelica D, Neyrinck AM, Fava F, Tuohy KM, Chabo C, Waget A, Delmée E, Cousin B, Sulpice T, Chamontin B, Ferrières J, Tanti JF, Gibson GR, Casteilla L, Delzenne NM, Alessi MC, Burcelin R. Metabolic endotoxemia initiates obesity and insulin resistance. Diabetes 2007; 56: 1761-1772.

74) Harbige LS. Fatty acids, the immune response, and autoimmunity: a question of n-6 essentiality and the balance between n-6 and n-3. Lipids 2003; 38: 323-341.

75) Brun P, Castagliuolo I, Di Leo V, Buda A, Pinzani M, Palu G, Martines D. Increased intestinal permeability in obese mice: new evidence in the pathogenesis of nonalcoholic steatohepatitis. Am J Physiol Gastrointest Liver Physiol 2007; 292: G518-525.

76) Rajilic-Stojanovic M, Jonkers DM, Salonen A, Hanevik K, Raes J, Jalanka J, de Vos WM, Manichanh C, Golic N, Enck P, Philippou E, Iraqi FA, Clarke G, Spiller RC, Penders J. Intestinal microbiota and diet in IBS: causes, consequences, or epiphenomena? Am J Gastroenterol 2015; 110: 278-287.

77) Cammarota G, Ianiro G, Bibbo S, Gasbarrini A. Gut microbiota modulation: probiotics, antibiotics or fecal microbiota transplantation? Intern Emerg Med 2014; 9: 365-373.