Food & Function

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: T. Requena, M. C. Martinez-Cuesta and C. Peláez, *Food Funct.*, 2018, DOI: 10.1039/C7FO01820G.

This is an Accepted Manuscript, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this Accepted Manuscript with the edited and formatted Advance Article as soon as it is available.

You can find more information about Accepted Manuscripts in the [author guidelines](#).

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard [Terms & Conditions](#) and the ethical guidelines, outlined in our [author and reviewer resource centre](#), still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this Accepted Manuscript or any consequences arising from the use of any information it contains.

1 **Diet and microbiota linked in health and disease**

2

3 T. Requena,* M.C. Martínez-Cuesta, C. Peláez

4

5 *Department of Food Biotechnology and Microbiology. Institute of Food Science*

6 *Research, CIAL (CSIC), Nicolás Cabrera 9, 28049 Madrid, Spain.*

7

8

9

10

11

12 *Corresponding author: Tel.: +34 91 0017900; E-mail address: t.requena@csic.es

13

Abstract

Diet has shaped microbiota profiles through human evolution. Traditional gut microbiomes are described to be driven by high levels of *Prevotella*. In the present, however, it is consistently described a lower microbial richness in urban industrialized populations compared with individuals living in rural settings, *Bacteroides* being predominant among urban-industrial gut microbiomes. Components of diet are highly influential in shaping the gut microbiota, being fiber, fat, proteins, polyphenols and micronutrients differentially metabolized by generalist and specialized microorganisms alone or through the phenomenon of cross-feeding. The progressive loss of microbial diversity over generations in industrialized societies along with the emerging increase of chronic non-transmissible diseases have been related to the decline in the consumption of dietary fiber. Diet and derived microbial metabolites have strong implications with the development of food associated diseases such as obesity and metabolic syndrome, malnutrition and eating disorders, intestinal inflammatory diseases and colorectal cancer, among others. Still, there is a need of further studies in order to identify microbiota-related biomarkers of risk for these disorders. In turn, healthy diets and specific nutritional interventions, including increase of dietary fiber and the consumption of probiotics and prebiotics, could be valuable for restoration of beneficial bacteria and microbiota diversity capable to shift from disease to health promoting states.

Keywords: Gut microbiota; Fiber; Diet-related diseases; Probiotics

38 **1. Introduction**

39 There is no place in the world without microorganisms. They live anywhere, any site
40 and any living being like plants, animals and humans. Human microbial colonization
41 occurs on the skin, in the genitourinary system, oral cavity and mostly in the intestinal
42 tract. In all these places they help maintaining physiological homeostasis by keeping a
43 symbiotic relationship with their hosts. Therefore, the history of human evolution
44 limited so far to the study of patterns of variation in human genes, has recently broaden
45 the spectrum to human microbes considering the symbiosis status of humans and its
46 resident microbiota as an evolutionary unit, the holobiont¹. According to Schnorr *et al.*²,
47 the microbiome represents our link to understanding deep evolutionary relationships
48 between human health and ancient ecologies. Indeed, the human microbiome may
49 rapidly adapt to shifts in human lifestyles, even in the absence of host genetic change.
50 Accordingly, microbes can be viewed as important players in crucial human events,
51 such as the rise of grain-based agriculture and the spread of human genetic variants that
52 facilitate lactose tolerance and dairying³.

53 The human microbiome influences metabolic, immune and defense systems in the
54 intestine and consequently, human health. They can also exert a major impact on
55 cognitive function and behavioral patterns and have likely played an important role in
56 human brain evolution which is our most defining trait⁴ and they are essential for
57 environmental interfacing⁵. Since we are born the composition of the gut microbiota is
58 highly influenced by major environmental factors such as diet, life-style including
59 physical exercise and exposure to antibiotics. But also, age, geographical location and
60 habits linked to traditional or Westernized long-term diets play a very relevant role in
61 the complexity of the gut microbiota. Intestinal microbiota relies on undigested or non-
62 digestible nutrients from the diet and intestine-mucosal turnover to keep their

63 population levels, whereas microbes and their metabolites in turn influence host energy
64 homeostasis and physiology. The human diet has changed over the times and the
65 industrialized trend has resulted in diminished consumption of the plant polysaccharides
66 that support the intestinal microbiota, the microbiota-accessible carbohydrates (MAC).
67 Consumption of dietary fiber in industrialized urban societies is certainly below the
68 recommended amounts in dietary guidelines, which is referred to as the ‘fiber gap’⁶, that
69 has led to the reduction of the overall degree of microbiome diversity and a progressive
70 loss of certain fiber-fermenting species over successive generations⁷. Changes in dietary
71 trends in industrialized societies revealing a decline in the amount of consumed fiber are
72 also associated with the emerging increase of chronic non-transmissible diseases, such
73 as obesity and associated metabolic diseases, inflammatory bowel diseases (IBD),
74 colorectal cancer, and allergies, among others⁸. Distant to obesity, subsisting
75 malnutrition and current eating disorders are closely related to diet and intriguingly
76 associated with microbial characteristics able to persist in the individuals^{9, 10} and to be
77 transmitted to germ-free mice transplanted with human microbiota¹¹. These examples
78 show that resilience of the microbiota determines whether a particular perturbation, e.g.
79 a change in nutrient availability, will permanently shift its stable state or whether it will
80 return to its initial homeostatic state, indicating that a distinct number of beneficial
81 (physiological) or detrimental (pathological) metabolic assembly states may exist¹².

82 In this review we analyze the existing data regarding the evolutionary patterns of the
83 human gut microbiota and the adapted use of specific dietary nutrients by the
84 microbiota. In addition, we describe the relevance of the gut microbiota in food-
85 associated health disorders and the way our gut microbiota can be modulated through
86 diet to improve human health.

87

88 **2. Long term dietary habits and geographical and ethnic factors that shape the gut**
89 **microbiota**

90 In the late 90's, studies using group-specific 16S rRNA-targeted oligonucleotide probes
91 discovered some characteristic features of the gut microbiota such as host specificity
92 and stability¹³. These studies were followed by metagenomic analysis that characterized
93 the microbiomes of several cohorts of American^{14, 15} and Japanese individuals¹⁶.
94 Overall, samples from adults were more complex than those from children but showed a
95 high functional uniformity regardless of age or sex. The first decade of the XXIth
96 century brought up a very fast progress in developments of high throughput sequencing
97 and bioinformatic technologies and this provided new knowledge on the composition
98 and functionality of the gut microbiome as an ecosystem and its variation across the
99 world. Early sequenced fecal metagenomes of individuals from four countries and their
100 comparison with published databases allowed grouping individuals in three high-level
101 clusters, the so called enterotypes that were not nation or continent-specific¹⁷. These
102 enterotypes were driven by groups of species that together contribute to the preferred
103 community compositions. Enterotype 1 was enriched in *Bacteroides* able to derive
104 energy primarily from carbohydrates and proteins through fermentation, enterotype 2
105 was enriched in *Prevotella*, a known mucin glycoproteins degrader, and enterotype 3
106 was dominated by *Ruminococcus* and *Akkermansia*, both mucin degraders of the
107 intestinal mucus layer. The authors suggested that these phylogenetic and functional
108 differences among enterotypes thus reflect different combinations of microbial trophic
109 chains with a likely impact on the synergistic inter-relations with the human hosts.
110 Moreover, they concluded that intestinal microbiota variation is generally stratified, not
111 continuous. This was in agreement with the contemporary work of Wu *et al.*¹⁸ who
112 sequenced fecal samples in a cross sectional study of 98 healthy volunteers and in a

control feeding study with 10 individuals. Fecal communities clustered into enterotypes distinguished primarily by levels of *Bacteroides* and *Prevotella*. Enterotypes were strongly associated with long-term diets, particularly protein and animal fat (*Bacteroides*) versus carbohydrates (*Prevotella*). In the interventional study, changes were significant and rapid, but the magnitude of the changes was modest and not sufficient to switch individuals between the enterotype clusters associated with protein/fat and carbohydrates.

In parallel, De Filippo *et al.*¹⁹ analyzed the gut microbiota of children aged 1-6 years old living in a village of rural Burkina Faso (Africa), in an environment close to that of Neolithic subsistence farmers and compared it with the microbiota of Italian children of the same age living in Florence in an environment typical of industrialized Europe. Burkina Faso children showed a significant enrichment in Bacteroidetes and depletion in Firmicutes with a unique abundance of *Prevotella* and *Xylanibacter*, completely lacking in the Italian children. This fact was concomitant with a high abundance of short chain fatty acids (SCFA) and a lower level of Enterobacteriaceae in African children compared to the Europeans. The authors hypothesized that gut microbiota coevolved with the polysaccharide-rich diets of African individuals allowing them to maximize energy intake from fiber while also protecting them from inflammations and noninfectious colonic diseases. More recently, Martínez *et al.*²⁰ found that inhabitants of non-industrialized regions in Papua New Guinea had greater bacterial diversity, lower inter-individual variation, vastly different abundance profiles, and bacterial lineages that were undetectable in the fecal microbiota of USA residents. It seems that community assembly in the Papua Guinean population is driven by bacterial dispersal as the main ecological process, which is not the case for the USA population. Mancabelli *et al.*²¹ have performed a meta-analysis of publicly available shotgun datasets of human fecal

138 samples collected from urbanized and traditional pre-agricultural populations and
139 concluded that industrialization has shaped the gut microbiota through the acquisition
140 and/or loss of specific gut microbes, thereby potentially impacting on the overall
141 functionality of the gut microbiome.

142 Broad populations of healthy humans representing different ages and culture
143 traditions including Guahibo Amerindians from Venezuela Amazonian, rural Malawi in
144 Africa and individuals in USA metropolitan areas, were sampled to discover how gut
145 microbiomes evolve within a lifespan and respond to diets and lifestyles²². The tribe
146 Hadza hunter-gatherers of Tanzania has been one of the most used populations for
147 answering evolutionary questions^{23, 24}. The diet of the Hadza is rich in complex
148 polysaccharides and the characterization of their gut microbiota showed that it is fully
149 adapted for broad spectrum metabolism, including enzymes for branched-chain amino
150 acid degradation and aromatic amino acid biosynthesis. Enrichment of *Prevotella*,
151 *Treponema* and unclassified Bacteroidetes, as well as a peculiar arrangement of
152 Clostridiales taxa, may enhance the Hadza's ability to digest and extract valuable
153 nutrition from fibrous plant foods. Targeted metabolomics approach was applied to
154 profile the fecal metabolome of this population allowing comparison with urban livings
155 in Italy as representative of people in the post-industrialized West²⁵. Data analysis
156 showed that when the diet is primarily plant-based, the fecal metabolome of the Hadza
157 is characterized by a distinctive enrichment in hexoses, glycerophospholipids,
158 sphingolipids and acylcarnitines, while depleted in the most common natural amino
159 acids and derivatives. Despite very little exposure to antibiotics, this population shows
160 antibiotic resistance genes, indicating the ubiquitous presence of environmentally
161 derived resistances. Interestingly, the Yanomami tribe in an Amerindian village in the
162 Amazon jungle of Venezuela with neither documented previous contact with Western

people nor known exposure to antibiotics, harbor bacteria that carry functional antibiotic resistance genes²⁶. These include genes conferring resistance to synthetic antibiotics and are syntenic with mobilization elements. In addition, these Yanomami harbored a microbiome with the highest diversity of bacteria and genetic functions ever reported in a human group. The authors suggest that Westernization significantly affects human microbiome diversity and that antibiotic resistance genes appear to be a feature of the human microbiome even in the absence of exposure to commercial antibiotics. Other hunter-gatherers communities from the Peruvian Amazon (Matsigenka) and traditional agricultural community from the Andean highlands (Tunapucoc) have been compared with USA urban-industrialized communities²⁷. As previously found, traditional gut microbiomes are driven by high levels of *Prevotella* while *Bacteroides* predominates among urban-industrial gut microbiomes. Hunter-gatherers formed a distinct sub-group among the traditional group showing high levels of *Treponema*, a genus widespread among non-human primates and traditional human communities. This fact suggests that they could be symbionts lost in urban-industrialized societies. Furthermore, Morton *et al.*²⁸ characterized the gut microbiota and parasites from Pygmy hunter-gatherer and Bantu farming and fishing populations in the rainforest of Southwest Cameroon. They found that both subsistence mode and the presence of the gut protozoa, *Entamoeba*, were significantly correlated with microbiome composition suggesting potential important interactions between the immune system, gut bacteria and gut parasites. Anwesh *et al.*²⁹ found very interesting results after studying two mongoloid tribal groups of Nicobar Islands in India who had migrated after the tsunami in 2004 from the remote to rural and urban areas. The gut microbiome of the cohort remaining at remote settings kept more diversity and stability than the other two cohorts and had higher levels of Bacteroidetes, with *Prevotella* as dominant genus. On the contrary, the

migrated urban cohort was dominated by *Bifidobacterium*. This is a remarkable example of gradual transition of the gut microbiome within the same ethnic community driven by dietary habits, socioeconomic status, environment and other aspects of lifestyle. In accordance with this, Gomez *et al.*³⁰ found that coexisting BaAka rainforest hunter-gatherers and their agriculturalist Bantu neighbors in the Central African Republic had distinct gut microbiomes. Hunter-gatherers harbored increased abundance of *Prevotella* and *Clostridium*, while the Bantu gut microbiome was dominated by Firmicutes. Moreover, comparisons with US Americans revealed Western-like features in the Bantu, including an increased abundance of predictive carbohydrate and xenobiotic metabolic pathways. It was concluded the existence of a gradient of traditional subsistence patterns in the two neighboring African groups that highlighted the adaptability of the microbiome in response to distinct diets and host environment.

The differences observed so far in microbiome composition and metabolomic profiles between communities living in rural settings and those living in industrialized countries, correlate with a consistent difference in microbial richness, being lower in urban industrialized populations compared to the rural ones. Recently, Gupta *et al.*³¹ provided a comprehensive review of geography, ethnicity and life-style-specific variations in gut microbiome of humans and how a gradual transition in compositional structure, along with a decrease in diversity, have driven gut microbiome through the three stages of human evolution: foraging, rural farming and industrialized urban Western life. The authors discuss factors playing a role in shaping the microbiome that comprise both host genetics and environmental factors, including diet. Modern life style factors involve the loss of dietary diversity over the past 50 years, due to decreased agrobiodiversity and decline in rearing varied edible plant varieties and animal breeds. One remarkable factor is the amount of fiber consumed that has declined in

213 industrialized societies. MAC found in dietary fiber have a crucial involvement in
214 shaping the microbial ecosystem. The use of humanized mice to model the impact of
215 diet on the gut microbiome has shown that the consumption of a low-fiber diet results in
216 the progressive loss of microbial diversity over several generations which is not
217 recoverable after the reintroduction of dietary MAC⁷. Besides, the dramatic increasing
218 use of antibiotics, caesarean section, water treatment and other sanitary practices in
219 developed countries have likely affected not only the transmission of pathogens but also
220 gut symbionts, thus diminishing gradually the microbiome diversity.

221

222 **3. Food ingredients and microbiota**

223 Although most dietary nutrients are absorbed in the small intestine, studies in ileostomy
224 subjects have described that about 17% protein, 2% digestible starch and 5% fat can
225 reach the colon³². In addition, limited microbial colonization and the constant peristalsis
226 make less feasible the interaction of the microbiota and food ingredients in the small
227 intestine. The largest interaction between diet and gut microbiota takes place at the large
228 intestine, where its content is also enriched in digestion-resistant dietary components,
229 mostly non-starch polysaccharides, which are consumed by microbiome consortia that,
230 in turn, contribute nutritional resources to the host primarily through short-chain fatty
231 acids (SCFA), vitamins and amino acids, among others (see Read and Holmes³³, for a
232 recent review).

233

234 **3.1. Carbohydrates**

235 The gut microbiota consumes the dietary non-digestible carbohydrates, including
236 resistant starch, plant cell-wall polysaccharides and oligosaccharides, that reach the
237 large intestine because the human digestive physiology lacks the capacity to process

238 them. Still, for many colonic bacteria, these complex carbohydrates are similarly
239 inaccessible and cannot be hydrolyzed or transported across membranes. Gut microbes,
240 then, not only compete for available carbohydrates, there is also advantageous
241 cooperation between bacteria to optimize these carbohydrates assimilation. Some act as
242 generalists³⁴ that are able to degrade a wide range of polysaccharides (Bacteroidetes),
243 and their by-products serve as important resources for others; there are also specialists
244 (Firmicutes) that are only able to assimilate a few selected carbohydrates.

245 The Bacteroidetes encode an average of 137 glycoside hydrolases per genome
246 compared to about 40 per genome in most Firmicutes³⁵, and almost 80% of the enzymes
247 in various Bacteroidetes are extracellularly located for the hydrolysis of large
248 polysaccharides. Although some Firmicutes species, such as *Roseburia intestinalis*, also
249 incorporates as high as 134 putative proteins for carbohydrate degradation, only 6 of
250 them are predicted to contain signal sequences for export to the surface of the cell³⁵.
251 Firmicutes are mostly specialized in specific transporters for simple carbohydrates³⁴.
252 *Bacteroides* represents the most prevalent genus of phylum Bacteroidetes in the human
253 gut. These bacteria contain unique gene clusters termed polysaccharide utilization loci,
254 which encode cell envelope-associated proteins involving glycoside hydrolases,
255 polysaccharide lyases, glycosyltransferases, carbohydrate esterases, etc., that enable
256 them to recognize and metabolize several plant derived polysaccharides³⁶. *Bacteroides*
257 *thetaiotaomicron* and *Bacteroides ovatus* are together capable of using all major glycan
258 classes found in plant cells, with the exception of cellulose³⁷.

259 The *Bifidobacterium* glycobioime represents one of the largest predicted enzyme
260 arsenals for carbohydrate metabolism so far identified among known gut commensals³⁸.
261 Members of this genus mostly employ ABC-transport systems and intracellular glycosyl
262 hydrolases to degrade dietary polysaccharides³⁹. *Bifidobacterium breve*, however, uses

cell-surface-anchored enzymes to degrade glycans such as starch, pullulan and glycogen⁴⁰. There are also specialized species such as *Bifidobacterium longum* subsp. *infantis* that contains enzymes dedicated to human milk oligosaccharide (HMO) utilization⁴¹. HMO represents an abundant (5-20 g/L) group of free glycans which contribute to the development of the neonatal microbiota since they are not digested through the gastrointestinal tract. The HMO show varying degree of polymerisation and different configurations of glycosidic linkages between galactose, glucose, N-acetylglucosamine, fucose and N-acetylneuraminic acid. The genomes of *Bifidobacterium*, mainly *B. longum* subsp. *infantis* and *Bifidobacterium bifidum* encode a broad spectrum of species-specific glycosyl hydrolases that metabolize particular HMO, such as fucosyl-lactose, sialyl-lactose and lacto-N-tetraose³⁸. *B. longum* subsp. *infantis* shows an ABC transporter of HMO to process them further intracellularly, whereas *B. breve* shows extracellular enzymes with fucosidase and sialidase activities. Overall, these HMO utilizing enzymes favor the *Bifidobacterium*-dominated intestinal community in breastfed infants⁴².

In general, *Bifidobacterium* species appear specialized for plant storage polysaccharides, such as starch and fructans, and oligosaccharides such as arabinoxylans, fructooligosaccharides (FOS) and galactooligosaccharides (GOS). For the utilization of inulin-type fructans, most *Bifidobacterium* species use intracellular β -fructofuranosidases, such as *B. longum* that hydrolyze FOS that are previously transported through the cell wall⁴³. GOS are imported into the cell to be further enzymatically processed, such as the transporter *LacS* used by *Lactobacillus acidophilus*⁴⁴. In addition to intracellular enzymes, *B. breve* and *B. longum* possess membrane-bound galactosidases that are active against longer-chain GOS^{45, 46}.

287 In addition to the mentioned specific glycolytic competences, the microbiota
288 utilization of dietary polysaccharides proceeds particularly through the phenomenon of
289 cross-feeding, where typically the Bacteroidetes serve as primary degraders of glycans
290 and the Firmicutes further process the released products. For example, the Firmicutes
291 species *Eubacterium rectale* upregulates oligosaccharide transporters in the presence of
292 *B. thetaiotaomicron* apparently to utilize the mono- or oligosaccharides or fermentation
293 end products derived from the Bacteroidetes species degradation of glycans⁴⁷. Another
294 example of cross-feeding was demonstrated between *E. rectale* and *B. longum* when
295 growing on arabinoxylan oligosaccharides (AXOS)⁴⁸. *B. longum* was only able to utilize
296 the arabinose side chains of the AXOS, releasing xylooligosaccharides (XOS). The co-
297 culture with *E. rectale*, which is capable of breaking down XOS extracellularly, allowed
298 both species to utilize all monosaccharide components. In addition, the acetate produced
299 by *B. longum* was used by *E. rectale* to produce butyrate.

300 Principal SCFA produced by gut bacteria in response to fiber metabolism are acetate,
301 propionate and butyrate. Acetate is a net fermentation product for most gut anaerobes
302 and consistently reaches the highest concentrations among the SCFA in the colon.
303 Lactate and succinate are also fermentation products, but they do not usually
304 accumulate to high levels as they are substrates for other bacteria to produce butyrate
305 and propionate, respectively. Butyrate-producing species belong mainly to the
306 Firmicutes families Ruminococcaceae, Lachnospiraceae and Clostridiaceae. Butyrate is
307 frequently produced via butyryl-CoA:acetate CoA-transferase with net consumption of
308 acetate⁴⁹. Propionate is formed mostly through the succinate pathway that is
309 characteristic of Bacteroidetes⁵⁰. Conversion of succinate to propionate also requires
310 vitamin B12. This metabolic cofactor and other corrinoids are provided by several
311 Firmicutes, Actinobacteria and Proteobacteria species⁵¹. SCFA are not only important

312 as energy source, but also regulate immune functions, intestinal hormone production
313 and lipogenesis. These microbial metabolites act as signaling molecules for maintaining
314 homeostasis and epithelial integrity and the amount and relative abundance of SCFAs
315 may be considered as biomarkers of a healthy status⁵².

316 Another characteristic example of cross-feeding between gut microbiota is related to
317 the H₂ produced from carbohydrate fermentation that can be used by methanogens to
318 produce methane, acetogens to produce acetate and sulfate-reducing bacteria to produce
319 H₂S³⁴. In addition, the consumption of H₂ allows energetically favorable fermentation of
320 propionate and the syntrophic mutualistic interaction between hydrogen-/formate-
321 producing and hydrogen-/formate-using microorganisms⁵³.

322

323 3.2. Protein

324 A significant amount (4 to 10 g/d) of nondigested protein and peptides may enter the
325 large intestine and is subjected to bacterial metabolism. Peptides seem to be preferred
326 over free amino acids by gut bacteria⁵⁴ and proteolysis appears to be higher in the distal
327 than the proximal colon region⁵⁵. Gut microbiota species such as *Clostridium*,
328 *Bacteroides* and *Lactobacillus*, contain up to hundreds of different identified
329 proteases⁵⁶. The best described proteolytic system of gut bacteria refers to *Lactobacillus*
330 that is characterized by a specialized cell-membrane attached proteinase, specific
331 peptide transporters and a coordinated assembly of intracellular peptidases that release
332 amino acids (see Liu *et al.*⁵⁷ for a comprehensive review). Amino acid catabolism
333 results in the production of phenolic compounds, amines, ammonia and branched-chain
334 fatty acids (BCFA)⁵⁸.

Bacteroidetes have major roles in proteolysis and in propionate formation from peptides⁵⁴. Also, bile-tolerant anaerobes such as *Bacteroides*, *Alistipes* and *Bilophila* are described to increase with consumption of animal-based protein⁵⁹. These authors found positive correlations between *Alistipes putredinis* and *Bacteroides* and products of amino acid catabolism. The animal protein-based diet has been associated with increased expression of genes for vitamin biosynthesis and the degradation of polycyclic aromatic hydrocarbons, which are recognized carcinogenic compounds. On the other hand, glutamate catabolism to gamma-aminobutyrate (GABA) is performed under acid stress by some intestinal bacteria⁶⁰, and can act as a neurotransmitter able to influence behavior⁴. Recently, Cervantes-Barragan *et al.*⁶¹ have demonstrated that intestinal *Lactobacillus reuteri*, together with a tryptophan-rich diet, can reprogram intraepithelial CD4⁺ T cells into immunoregulatory T cells that promote tolerance to dietary antigens.

3.3. Fat

Animal-based diets are often high in fat, in addition to protein, and low in complex carbohydrates. The gut microbiota metabolizes dietary fats producing diacylglycerols from polyunsaturated fats and convert primary bile acids into secondary bile acids⁶². Caesar *et al.*⁶³ have described that the genera *Bacteroides*, *Turicibacter* and *Bilophila* were increased in lard-fed mice, while *Bifidobacterium*, *Lactobacillus*, *Streptococcus* and *Akkermansia muciniphila* were increased in fish-oil-fed mice. *Akkermansia* has been highlighted as a potential mediator of the improved inflammatory and metabolic phenotype of mice fed fish oil and to protect against diet-induced obesity^{64, 65}.

Data from human intervention studies suggest that dietary fat indirectly modulates intestinal microbiota composition based on its impact on bile acid secretion. It is known

that high dietary fat consumption stimulates the secretion of primary bile acids that can enter into the colon where they are further metabolized to secondary bile acids by the gut microbiota⁶⁶. The high fat intake has been described to increase bile-resistant taxa such as *Bilophila wadsworthia*, *A. putredinis* and *Bacteroides*⁵⁹. *Bilophila*, a member of the H₂S-producing Desulfovibrionaceae which generally comprises less than 0.1% of the normal human gut microbiota, include species that are bile resistant, non saccharolytic and sulfate-reducers⁶⁷. These bacteria show a unique ability to perform anaerobic respiration using taurine-derived sulfite as an electron acceptor, resulting in the formation of H₂S as a by-product⁶⁸. Colonization of germ-free mice with *B. wadsworthia* has been described to be only established in mice fed saturated fat diets and not with PUFA or low fat diets⁶⁹.

Regarding PUFA, the ability of gut bacteria to metabolize dietary PUFA in vivo was demonstrated in mice⁷⁰. *Roseburia* spp., *Butyrivibrio fibrisolvens* and *Propionibacterium freudenreichii* subsp. *shermani* show linoleate isomerase activity with the formation of conjugated linoleic acid (CLA) and vaccenic acid as metabolic products⁷¹. Dietary n-3 PUFA intake has been positively associated with *Lactobacillus* and *Bifidobacteria* abundance⁷². Lam *et al.*⁷³ have compared the effect of saturated, n-6 or n-3 fatty acids on mice microbiota. The results confirmed the association of the H₂S-producing genera *Bilophila* and *Desulfovibrio* with saturated fat diets, whereas these bacteria remained relatively stable in the n-6-fat fed mice and modestly reduced in the n3-fat mice. Therefore, literature data identify *Bilophila* as a signature of dietary fat intake and impairment of gut barrier due to the H₂S harmful effect on colonocytes⁷⁴.

382

383 3.4. Polyphenols

384 Dietary polyphenols, which include catechins, flavonols, flavanones, anthocyanins,
385 proanthocyanidins and phenolic acids, from fruits, seeds, vegetables, tea, cocoa
386 products and red wine, among others, can reach amounts above 2 g per day⁷⁵.
387 Oligomeric and polymeric polyphenols are not absorbed in the small intestine and reach
388 the colon where they can modulate the gut microbiota composition and function.
389 Phenolic compounds can show antibacterial effects due to interferences with cell
390 membrane functions and with bacterial energy metabolism⁷⁶. Flavan 3-ols, such as
391 epigallocatechin gallate, form complexes with bacterial membranes. Tannins, which
392 have the ability to precipitate proteins, can inhibit some extracellular bacterial enzymes,
393 complex metal ions and impair substrates assimilation⁷⁷. In addition to the antimicrobial
394 effects of polyphenols, intestinal microbiota modulation is also affected by the
395 capability of some microbial species to metabolize them. Some *Lactobacillus* and
396 *Bifidobacterium* strains have been reported to have rhamnosidase and beta-glucosidase
397 activities processing native polyphenols in order to release the corresponding
398 aglycones^{78, 79}. *Bacteroides*, *Eubacterium*, *Enterococcus* and *Blautia* can deconjugate
399 rutin to release the aglycone quercetin⁸⁰.

400 An outstanding catabolic reaction of gut microbiota on polyphenols is the breaking
401 of carbon rings. These catabolic reactions are carried out under anaerobic conditions by
402 *Gordonibacter*, *Flavonifractor*, *Eubacterium* and *Eggerthella*⁷⁷. *Lactobacillus*
403 *plantarum* has the capability to initiate the catabolism of polyphenols via galloyl-
404 esterase, decarboxylase and benzyl alcohol dehydrogenase activities and by the
405 cleavage of the heterocyclic ring of monomeric flavan-3-ols^{81, 82}. These reactions convert
406 non-absorbable flavan-3-ols and condensed tannins into readily-bioavailable potentially
407 bioactive metabolites. The hydrolysis of ellagitannins, present for example in
408 pomegranates, releases ellagic acid, which can be metabolized by *Gordonibacter* spp.

409 into several structurally related urolithins⁸³. The glycosidic-isoflavone daidzin, that is
410 predominantly found in soy products, can be metabolized to equol by *Enterococcus*,
411 *Lactobacillus*, *Slackia*, *Bifidobacterium* and *Eggerthella*⁸⁴; however, only
412 approximately one-third of human individuals are estimated to harbor intestinal
413 microorganisms capable of producing equol⁸⁵. The lignans are metabolized to the
414 bioactive metabolites enterodiol and enterolactone by a multistep pathway involving
415 several gut bacteria, including *Enterococcus*, *Eggerthella*, *Blautia*, *Eubacterium*,
416 *Clostridium* and *Lactonifactor*⁷⁷. Recently, Gaya *et al.*⁸⁶ described for the first time the
417 production of enterodiol from lignan extracts by a *Bifidobacterium adolescentis* strain.

419 3.5. Micronutrients and food additives

420 Vitamins or other dietary antioxidants that have reduction–oxidation mediating
421 functions exert modulating effects on the strict anaerobic gut microbiota, since oxygen
422 and free oxygen radicals rapidly oxidize their sensitive enzyme systems⁸⁷. Dietary
423 riboflavin can reach the colon when administered in amounts over 30 mg due to the
424 saturable transport process that takes place at the proximal small intestine⁸⁸. The
425 supplementation of a group of adult volunteers with 100 mg riboflavin for 14 days have
426 shown an increase of *Faecalibacterium prausnitzii* and *Roseburia*, and a decrease in *E.*
427 *coli*, indicating an improvement in the redox state in the gut⁸⁹. The authors
428 demonstrated that *F. prausnitzii* can exploit extracellular riboflavin to transfer electrons
429 to oxygen to lower the redox potential and survive in moderately oxygenized
430 environments. Vitamin A deficiency has been described to exert a relevant effect on
431 bacterial community structure, with *Bacteroides vulgatus* increasing its abundance in
432 the absence of vitamin A⁹⁰. On the other hand, Vitamin C and E deficiencies inhibit the
433 abundance of *Bacteroides*, whereas vitamin B6 is essential for aminotransferase

434 metabolism in *E. rectale*⁹¹. For minerals, magnesium requirements are higher for Gram-
435 positive than for Gram-negative bacteria, and are relevant in the physiology of
436 bifidobacteria⁹².

437 Artificial non-caloric sweeteners consumption is increasing in industrialized
438 countries. Most of these sweeteners are not digested by the human gastrointestinal tract
439 and reach the colon where they can be metabolized by the microbiota. The microbiota
440 of saccharin-consuming mice shows an increase in *Bacteroides* and a decrease of *L.*
441 *reuteri*, *A. muciniphila* and some Clostridiales⁹³. The microbial changes caused by some
442 artificial sweeteners seem to have a functional consequence, as germ-free mice that are
443 colonized with gut microorganisms from sweeteners-treated mice have impaired
444 glucose homeostasis⁹³. However, information describing the microbial metabolic
445 transformation of these additives is scarce.

446 Similarly, food emulsifying agents have detergent-like properties and there are
447 studies that indicate that some of these additives may have an effect on the composition
448 of the gut microbiota⁹⁴. Controlled feeding of carboxymethylcellulose and polysorbate-
449 80, two emulsifying agents, to mice resulted in a reduction in the abundance of
450 Bacteroidales and an increase in the abundance of the mucolytic bacteria *Ruminococcus*
451 *gnavus*⁹⁵.

452

453 **4. Diet-associated diseases and microbiota**

454 The emerging increase of chronic non-transmissible diseases, such as obesity and
455 associated metabolic diseases, inflammatory bowel diseases, colorectal cancer, allergies
456 and autoimmune disorders, has been reported to be closely linked with microbiota-diet
457 interactions⁹⁶. In turn, the metabolic activities of the gut microbiota and its link with
458 immune homeostasis and modulation of mucosal inflammation have important health

consequences⁵. In this review, we will focus on the interplay between diet and microbiota with regards to its influence on risk of obesity and metabolic diseases, undernutrition and eating disorders, inflammatory bowel diseases and colorectal cancer.

4.1. Obesity and metabolic diseases

Obesity is a multifactorial condition which is influenced by a complex interplay of genetic, endocrine and environmental mechanisms. Among these, the role of the microbiota on the intersection between diet and obesity has emerged as the focus of numerous studies (see Duranti *et al.*⁹⁷ for a comprehensive review). Gut microbiota transplantations in mice and in humans indicate that a specific gut microbiota composition can be the cause and not just the consequence of the obese state and metabolic disease^{98, 99}. Studies showing that germ-free (GF) mice following consumption of a Western-style, high-fat, sugar-rich diet are protected against diet-induced obesity and exhibit reduced white adipose tissue (WAT) inflammation and insulin resistance^{100, 101}. Nevertheless, the resistance to diet-induced obesity in GF mice appears to be highly dependent on the macronutrient composition of the diet^{102, 103}. Microbiota dysbiosis is thought to promote obesity through different mechanisms such as an improved capacity for energy harvest and storage as well as enhanced gut permeability and inflammation. Although initial and further reports showed large phylum level microbiota shifts, an increase in Firmicutes and decrease in Bacteroidetes associated to obesity^{15, 104}, some other studies have shown no difference or even an opposite result¹⁰⁵. It is worth to note that the increase of one phylum with respect to the other was associated with a higher presence of enzymes for complex carbohydrate degradation and fermentation¹⁰⁶. More recently, it has been suggested that human genetics shape the gut microbiome, being a specific heritable bacterial taxon,

484 Christensenellaceae, demonstrated to be associated with obesity, and proposed as a
485 novel microbial biomarker for obesity¹⁰⁷. Methanogenic Archaea may also contribute to
486 altered metabolism and weight gain in the host¹⁰⁸; nevertheless, other studies have
487 demonstrated lower levels of *Methanobrevibacter* in overweight and obese human
488 volunteers¹⁰⁹. Besides, even the fungal microbiota -mycobiome- has been suggested to
489 differ in obese and non-obese counterparts, since *Mucor racemosus* and *Mucor fuscus*
490 were found to be the species more represented in non-obese subjects¹¹⁰.

491 In addition to community structure changes, differences in microbiota functionality
492 have also been reported in obesity. It has been suggested that the obese microbiome is
493 enriched for metabolic pathways involved in the generation of SCFA, showing
494 overweight and obese individuals higher fecal SCFA concentrations than their lean
495 counterparts¹¹¹. Nevertheless, the interactions between amount and ratio of SCFA, gut
496 microbiota and its role in obesity are quite complex because of the contradictories
497 reports to date. SCFA not only may enhance energy harvest and contribute to excess
498 lipogenesis in the liver, but also concurrently could reduce inflammation and contribute
499 to epithelial barrier integrity and satiety⁵². Thus, Den Bensten *et al.*¹¹² have reported
500 beneficial metabolic effects of SCFA as protection against high fat diets (HFD) induced
501 obesity and improvement of insulin sensitivity. Besides, metagenomic studies have
502 identified butyrate-producing bacteria that are negatively associated with obesity and
503 subsequent insulin resistance such *Roseburia* and *F. prausnitzii*, in obese individuals¹¹³.

504 HFD induced changes in the community structure and diversity of the gut microbiota
505 and further metabolic perturbations appear to be dependent on the amount and type of
506 fat content. Diets rich in long-chain saturated fatty acids decrease the abundance of *A.*
507 *muciniphila*, which plays a preventive role in the development of diet-induced obesity
508 by improving gut barrier function and glucose metabolism⁶⁴, while select for the

mucosal sulphite-reducing pathobiont *B. wadsworthia*⁶⁹. Additionally, it has been shown that mice fed a lard diet have increased inflammation in WAT and impaired insulin sensitivity compared to mice fed fish oil, which was partly attributed to distinct microbiota composition⁶³. Mice fed oil had increased levels of taxa from the genera *Lactobacillus* and *A. muciniphila*; by contrast, mice fed lard had increased levels of taxa related to *Bilophila*.

Obesity increases cardiovascular disease through different risk factors, such as elevated triglycerides and high low-density lipoprotein-cholesterol and elevated blood glucose and insulin levels. Rabot *et al.*¹¹⁴ have described that gut microbiota rich in Bacteroidetes protect mice from developing severe glucose intolerance independent of body weight. Animal studies suggest that species such as *Clostridium ramosum* and *Enterococcus cloacae* promote obesity in gnotobiotic mouse models and are associated with symptoms of metabolic disease, whereas bifidobacteria and *A. muciniphila* are associated with favorable phenotypes in conventional mice¹¹⁵. Chronic increased production of acetate by an altered gut microbiota in rodents has demonstrated to activate the parasympathetic nervous system, which, in turn, promotes increased liver and muscle insulin resistance, increased ghrelin secretion, hyperphagia, hyperlipidaemia, obesity and metabolic diseases¹¹⁶.

Trimethyl amine N-oxide (TMAO), a microbial metabolite generated from dietary phospholipid phosphatidylcholine (lecithin) and L-carnitine has recently emerged as a candidate risk factor for cardiovascular disease via atherosclerosis development and other adverse health outcomes^{117, 118}. Phospholipid phosphatidylcholine is enriched in foods such as red meat, eggs, milk and certain fish. Vegans and vegetarians do not only have lower fasting baseline levels of red meat-derived proatherogenic TMAO compared

533 to omnivores, but their microbiota also have lower capacity to synthesize it from
534 ingested carnitine¹¹⁹.

535 These findings suggest that the beneficial or detrimental health effects of dietary
536 components not only depend on their intake rate but also on the individual's microbiota.
537 Still, there is a need of further studies in order to identify microbiota-related biomarkers
538 of risk for obesity and metabolic diseases.

539

540 **4.2. Undernutrition and eating disorders**

541 Undernutrition involves a deficiency of calories or essential nutrients. It is associated
542 with reduced immune function, poor growth in height and neurocognitive deficits and
543 with an altered gut microbiota¹²⁰. Undernutrition associated microbiota is characterized
544 by decreased fecal microbial community richness¹¹ and reduction of strictly anaerobic
545 species, in particular *Methanobrevibacter smithii*, and an enrichment in potentially
546 pathogenic Proteobacteria, Fusobacteria and *Streptococcus gallolyticus*¹²¹. The
547 transplantation into GF mice of the kwashiorkor microbiome in combination with a diet
548 low in protein and fat, designed to mimic the donors' diet, result in marked weight loss
549 in the recipient mice, along with perturbations in carbohydrate and amino acid
550 metabolism¹¹. Blanton *et al.*¹²² observed that the introduction into young GF mice of *R.*
551 *gnavus* and *Clostridium symbiosum*, together with the microbiota from undernourished
552 donors, ameliorated growth and metabolic abnormalities in the recipient animals. The
553 authors stated that microbiota immaturity is causally related to undernutrition.

554 Another disorder resulting in severe malnutrition is anorexia nervosa (AN). The diet
555 of AN patients is characterized by a significant low energy intake, with high restriction
556 in consumption of fats and carbohydrates⁹. These authors observed an altered
557 composition of the gut microbiota in AN patients characterized by a significant increase

of Enterobacteriaceae and *M. smithii* compared with healthy controls, whereas *Roseburia*, *Ruminococcus* and *Clostridium* were depleted. Microbiological differences were associated with reduction in total SCFA, butyrate and propionate in AN patients. The gut dysbiosis observed in AN patients, which may not improve after weight gain¹²³, could sustain the persistence of alterations that eventually result in relapses after renourishment and psychological therapy. This resembles the intestinal microbiome signature that persists after successful dieting and contributes to faster weight regain and metabolic aberrations upon re-exposure to obesity-promoting conditions, commonly referred to as the “yo-yo effect”¹⁰.

4.3. Inflammatory bowel diseases

The etiology and pathogenesis of IBD, including Crohn’s disease (CD) and ulcerative colitis (UC) have remained unclear. Nevertheless, it becomes clear that diet and the interaction between diet and microbiome contribute significantly to the onset of the disease¹²⁴. Diet can affect inflammatory processes and the immune system directly and also through mechanisms involving gut microbiota. Recently, functional characterization of IBD-associated gut dysbiosis in gnotobiotic mice have showed that dysbiosis potentially contributes to the pathogenesis of IBD by augmenting host proinflammatory immune responses¹²⁵.

Gut dysbiosis in patients with IBD is defined as a reduction of beneficial commensal bacteria and an enrichment of potentially harmful commensal bacteria (pathobionts). Moreover, a dysbiosis of fungal microbiota in IBD patients' faeces has recently been observed¹²⁶. In this regard, IBD patients have reduced microbiota diversity along with decreases in Firmicutes and Bacteroidetes, whereas Proteobacteria and Actinobacteria are increased considerably. In addition, an increased load of aggressive bacteria are

583 attached to the intestinal mucus layer in IBD patients; thus, the adherent-invasive *E. coli*
584 (AIEC) pathovar, and *Fusobacterium varium* are in higher richness in IBD patients¹²⁷,
585 ¹²⁸. A reduction of bacteria that produce SCFA such as *Roseburia* and *F. prausnitzii* has
586 also been reported in IBD patients, which may contribute to the intestinal
587 inflammation¹²⁹. Besides, it has been stated that enzymes enriched in IBD microbiomes
588 are more frequently involved in membrane transport, which could support a “leaky gut
589 hypothesis” contributing to the disease state¹³⁰.

590 Diets high in animal protein of red and/or processed meat, saturated fats and food
591 additives including sweeteners, emulsifiers, preservatives, are associated with an
592 increased risk of IBD. Food additives can disturb the host-microbiota relationship
593 resulting in a microbiota with enhanced mucolytic and pro-inflammatory activity that
594 promotes intestinal inflammation⁹⁵. The triggering of symptoms in IBD patients have
595 also been associated to the consumption of indigestible and poorly absorbed short-chain
596 carbohydrates¹³¹. In contrast, diets rich in fish n-3 PUFA and high n-3:n-6 PUFA ratio
597 along with the consumption of fermentable fibers and fruit and vegetables lower the risk
598 for IBD¹³².

599 Deficiency of dietary vitamins and minerals are thought to be involved in the
600 pathogenesis of IBD¹³³. Vitamin D plays a role in signaling on barrier integrity and
601 innate and adaptive immunity in the gut, as well as on the modulation of commensal
602 microbiota composition^{134, 135}. Incidence of IBD is higher in the Northern hemisphere
603 where sunlight exposure is lower^{136, 137}. However, data from observational studies are
604 insufficient to determine whether lower vitamin D causes IBD, or it is the result of
605 nutrient malabsorption.

606 Diet-induced changes on bile acids could also affect the development of IBD; thus,
607 consumption of saturated milk-derived fat diets but not polyunsaturated fat or low-fat

608 diets evidenced the released of a large quantity of taurocholic acid that in turn promotes
609 the bloom of *B. wadsworthia* associated with the increased incidence of colitis⁶⁹. This
610 sulphite-reducing pathobiont can use sulfur-containing foods as an efficient source for
611 the generation of H₂S. This metabolite has been shown to interfere with butyrate
612 utilization of colonocytes and to have adverse inflammatory effects in the colon¹³⁸.
613 Nevertheless, other studies suggest that H₂S promotes wound healing in rodents with
614 colitis facilitating correction of microbiota biofilm dysbiosis and mucus layer
615 reconstitution¹³⁹.

616

617 4.3. Colorectal cancer

618 Diet and nutritional habits have been strongly linked to colorectal cancer (CRC).
619 Epidemiological studies have revealed on one side that consumption of fruits,
620 vegetables and whole grains reduces CRC risk. On the other side, there is currently
621 overwhelming indication that consumption of red and processed meat as well as animal
622 fat, typical of Western-style diets, increases CRC risk¹⁴⁰. Recent studies highlighted that
623 associations between meat intake and CRC differ depending on meat type, sex and
624 tumor location in the bowel¹⁴¹.

625 It is worth to note that different studies revealed that fecal microbiota only partially
626 reflects mucosal microbiota in CRC^{142, 143}. Microbial diversity was shown to be
627 significantly lower in the tumor tissue than the noncancerous one; in cancerous tissue,
628 Lactobacillales were enriched, whereas *Faecalibacterium* were reduced. Moreover, the
629 microbial structure of the intestinal lumen and cancerous tissue differed significantly¹⁴⁴.
630 Regarding mucosa-adherent bacteria, these authors observed that *Bifidobacterium*,
631 *Faecalibacterium* and *Blautia* were reduced in CRC patients, whereas *Fusobacterium*
632 and *Phorphyromonas* were increased.

633 Some bacteria can initiate carcinogenesis via the production of toxins that can
634 damage DNA. In this regard, certain strains of *E. coli* containing the polyketide
635 synthase (*pks*) pathogenicity island are overrepresented in CRC cases and might have a
636 causative role in human CRC development¹⁴⁵. Boleij *et al.*¹⁴⁶ also found that the
637 detection of enterotoxigenic *Bacteroides fragilis* toxin increased in the mucosa of late-
638 stage CRC.

639 In the last years, several specific members of the gut microbiome have become of
640 particular interest in CRC. In this regard, abundance and detection rate of species
641 belonging to *Fusobacterium*, *Bacteroides* and *Methanobacteriales* may provide a
642 potential marker for early detection of CRC¹⁴³. Colon cancer risk is also influenced by
643 the balance between microbial production of health-promoting metabolites such as
644 butyrate and potentially carcinogenic metabolites such as secondary bile acids¹⁴⁷.
645 Butyrate, a chemoprotective agent, acts as a histone deacetylase (HDAC) inhibitor
646 capable of decreasing proliferation and increasing apoptosis in CRC cells; but butyrate
647 could also diminish tumorigenesis by attenuating inflammation and colonocyte
648 permeability and maintaining barrier function of the epithelium. Additionally, H₂S
649 interferes with butyrate utilization of colonocytes and has been linked to IBD and
650 CRC¹⁴⁸. Other SCFA such as propionate could act also as a HDAC inhibitor¹⁴⁵. With
651 regard to bile acids, epidemiological data have shown that tumor promoting activity of
652 Western-style/high fat diet is associated with increased colonic bile acid concentrations
653 and higher fecal bile acid levels, as detected in patients diagnosed with CRC¹⁴⁹.

654 Recently, other metabolites related to cellular respiration, carbohydrate, lipid, protein
655 and nucleotide metabolism have been shown to be significantly altered in CRC; thus,
656 metabolomic profiling could distinguish CRC patients from normal controls and will be
657 a promising tool in early noninvasive diagnosis of CRC¹⁵⁰. Another important link

658 between the gut microbiome and CRC is inflammation. A recent study showed that
659 CRC-associated bacterial clusters are differentially correlated with mucosal gene-
660 expression profiles for host immunoinflammatory responses¹⁴².

661

662 **5. Microbiota modulation in food-associated disorders through dietary**

663 **interventions**

664 As stated in previous sections, diet is the main driver in profiling the human gut
665 microbiota and disruption of the gut microbiota balance and reduced microbiota
666 diversity are related with diet-related diseases. Therefore, it seems conceivable to
667 consider diet as a means to correct microbiota dysbiosis. Lawrence and Hyde¹⁵¹ have
668 proposed a self-named Mediterranean style dietary protocol called *The Gut Makeover*,
669 which is intended to restore gut bacteria balance by restricting processed high grain
670 carbohydrate foods, sugar, and artificial sweeteners, together with increasing the
671 consumption of vegetables and fermented foods. The study by Lawrence and Hyde,¹⁵¹
672 however, described an uncontrolled observational study of self-reported symptoms and
673 lacked the corresponding analyses to support the possible microbial changes associated
674 to the observed improving in physical and emotional wellbeing.

675 The low-fermentable oligo-, di-, and monosaccharide and polyol (FODMAP) diet is
676 a two-phased dietary intervention, with strict reduction of all slowly absorbed or
677 indigestible short-chain carbohydrates followed by reintroduction of specific
678 FODMAPs according to tolerance that is increasingly used in the clinical setting for
679 IBD patients^{132, 152}. Specialists, however, are proclaiming that excessively restrictive
680 diets may negatively impact the gut microbiota and nutritional status of the patients and
681 carry risks of fostering disordered eating and reducing beneficial bacteria such as
682 bifidobacteria and butyrate-producing bacteria¹⁵³. Furthermore, as previously stated, a

low MAC diet over several generations would cause a progressive loss of microbiota diversity, which is not recoverable after the reintroduction of dietary MAC⁷. In addition, MAC deficiency leads to a rapid increase in abundance of mucin-degrading bacteria and the development of inflammatory diseases¹⁵⁴.

Regarding diet-related diseases, probiotics, prebiotics and synbiotics have been particularly assayed in studies of obesity and metabolic syndrome^{155, 156}. Although not stated yet as probiotic species, administration of live *A. muciniphila* has demonstrated to reduce adiposity, inflammatory markers, insulin resistance and improved gut barrier in mice fed HFD⁶⁴. Recently the species has been supplemented to individuals with excess body weight, once demonstrated its safety and tolerability and that pasteurized *A. muciniphila* showed remarkable benefits on body weight gain, fat mass gain and glucose intolerance in HFD-fed mice¹⁵⁷. Among commercially available probiotics, *Lactobacillus* and *Bifidobacterium* strains have been extensively evaluated for a potential anti-obesity role^{158, 159}. Although not fully elucidated, the mechanisms by which probiotics exert their anti-obesity effects call attention to modulation of lipid and glucose metabolism and inflammation¹⁵⁵. Some metabolites produced by probiotic strains, such as the anti-obesogenic CLA by *B. breve*, contribute to reduce levels of liver triglycerides in the host and increase tissue concentrations of bioactive long-chain n-3 PUFA, including increase of docosahexaenoic acid in brain¹⁶⁰.

Prebiotics, and particularly fructans, have demonstrated that are able to counteract several metabolic alterations linked to obesity, including hyperglycemia, inflammation, insulin resistance and hepatic steatosis and to lower the postprandial glycaemia and appetite, mostly through their interaction with the gut microbiota and particularly bifidobacteria¹⁶¹. In addition, prebiotics can also affect health benefits independently of their microbial effect. Bindels et al.¹⁶² have demonstrated improvements in insulin

708 levels exerted by dietary resistant starch that involve alterations in the bile acid cycle
709 and adipose tissue immune modulation. The authors propose that high doses of resistant
710 starch induce release of metabolites from bacterial fermentation, leading to a decrease in
711 body weight and/or fat mass via a GLP1-PYY-dependent mechanism¹⁶³ and when fed at
712 lower doses, resistant starch improves insulin resistance independently of the gut
713 microbiota.

714 Other food ingredients, such as polyphenols, have shown anti-obesity effects linked
715 to interaction with the gut microbiota⁹⁴ and the called “yo-yo effect” characterized by a
716 post-diet weight-rebound¹⁶⁴. These authors supplemented mice with the microbiome-
717 derived flavonoids apigenin or naringenin (so-called post-biotics) that resulted in
718 suppressing the weight rebound during the second course of high fat diet.

719 On the other side of eating disorders, nutritional rehabilitation is a key component to
720 reverse malnutrition. Probiotics and prebiotics have resulted functional in relieving the
721 gastrointestinal and psychological symptoms that are associated to eating disorders and
722 the consumption of low-caloric diets¹⁶⁵. A combination of cultured probiotics
723 candidates, identified in healthy children that were missing in Kwashiorkor children,
724 belonging to 12 species from the genera *Alistipes*, *Anaerostipes*, *Bacillus*,
725 *Bifidobacterium*, *Lactobacillus*, and *Weissella*, among others, have been proposed by
726 Tidjani Alou et al.¹²¹ to restore a healthy gut microbiota in malnourished children.

727 On the role of probiotics and prebiotics in CRC prevention, there are in vitro and
728 preclinical studies that show the ability of some probiotic strains to bind or degrade
729 mutagenic amines and reduce activity of enzymes potentially involved in transforming
730 pro-carcinogens into active carcinogens and the capability to prevent or reduce aberrant
731 crypt foci in animal models when consuming *Lactobacillus* and *Bifidobacterium*¹⁶⁶.
732 Based on that the immune system plays a central role in the control of cancer cells, the

733 potential anticancer activities of probiotics and prebiotics have also been examined in
734 the context of immune system modulation¹⁶⁷.

735
736 **6. Concluding remarks**

737 In summary, it seems worldwide accepted that geographical location, life style and long
738 term dietary patterns influence the microbial diversity and the abundance of the two
739 well-known *Bacteroides* and *Prevotella* enterotypes of the gut microbiome. However,
740 there is a debate whether enterotypes should be seen as discrete clusters, which could
741 mask important within-cluster variation in critical microbial taxa related to a disease
742 state, or gradients^{168, 169}. Microorganisms adapt to the gut environment in multiple ways
743 interacting among them and with the host. This can only be explained by the capability
744 of carrying out the same functions through different metabolic pathways that enable
745 them to adapt and quickly react to dietary changes. Therefore, metatranscriptomic,
746 metaproteomic and metabolomic analyses of fecal samples are valuable to understand
747 functional aspects of the gut microbiota^{170, 171}. Promoting the resilience of beneficial
748 microbiota assemblies has also been proposed for microbiome-directed precision
749 medicine by the stratification of patients according to the properties of their microbial
750 communities¹².

751 Taken into account the points already mentioned in this review, diet has a role in the
752 development of some pathologies and many of them are also associated with dysbiosis
753 in the composition and/or functionality of the intestinal microbiome. Regarded diet as a
754 whole, it could be stated that increased MAC intake represents a nutritional strategy that
755 may limit excessive formation of microbial toxic metabolites and a non-return loss in
756 gut microbiota. Probiotics and prebiotics would be also valuable for restoration of

757 beneficial bacteria and microbiota diversity capable to shift from disease to health
758 promoting states.

759

760 **Acknowledgements**

761 This work was supported by the Spanish MINECO (Project AGL2016-75951-R) and
762 CYTED (Project P916PTE0233).

763

764 **References**

765

766 1. K. R. Theis, N. M. Dheilly, J. L. Klassen, R. M. Brucker, J. F. Baines, T. C. Bosch, J. F.
767 Cryan, S. F. Gilbert, C. J. Goodnight, E. A. Lloyd, J. Sapp, P. Vandenkoornhuyse, I. Zilber-
768 Rosenberg, E. Rosenberg and S. R. Bordenstein, Getting the Hologenome Concept
769 Right: an Eco-Evolutionary Framework for Hosts and Their Microbiomes, *mSystems*,
770 2016, **1**.

771 2. S. L. Schnorr, K. Sankaranarayanan, C. M. Lewis, Jr. and C. Warinner, Insights into
772 human evolution from ancient and contemporary microbiome studies, *Current opinion*
773 *in genetics & development*, 2016, **41**, 14-26.

774 3. J. Burger, M. Kirchner, B. Bramanti, W. Haak and M. G. Thomas, Absence of the
775 lactase-persistence-associated allele in early Neolithic Europeans, *Proceedings of the*
776 *National Academy of Sciences of the United States of America*, 2007, **104**, 3736-3741.

777 4. J. R. Kelly, C. Minuto, J. F. Cryan, G. Clarke and T. G. Dinan, Cross Talk: The Microbiota
778 and Neurodevelopmental Disorders, *Frontiers in neuroscience*, 2017, **11**, 490.

779 5. C. A. Thaiss, N. Zmora, M. Levy and E. Elinav, The microbiome and innate immunity,
780 *Nature*, 2016, **535**, 65-74.

781 6. E. C. Deehan and J. Walter, The Fiber Gap and the Disappearing Gut Microbiome:
782 Implications for Human Nutrition, *Trends in endocrinology and metabolism: TEM*,
783 2016, **27**, 239-242.

784 7. E. D. Sonnenburg, S. A. Smits, M. Tikhonov, S. K. Higginbottom, N. S. Wingreen and J. L.
785 Sonnenburg, Diet-induced extinctions in the gut microbiota compound over
786 generations, *Nature*, 2016, **529**, 212-215.

787 8. E. C. Deehan, R. M. Duar, A. M. Armet, M. E. Perez-Munoz, M. Jin and J. Walter,
788 Modulation of the Gastrointestinal Microbiome with Nondigestible Fermentable
789 Carbohydrates To Improve Human Health, *Microbiology spectrum*, 2017, **5**.

790 9. F. Borgo, A. Riva, A. Benetti, M. C. Casiraghi, S. Bertelli, S. Garbossa, S. Anselmetti, S.
791 Scarone, A. E. Pontiroli, G. Morace and E. Borghi, Microbiota in anorexia nervosa: The
792 triangle between bacterial species, metabolites and psychological tests, *PloS one*,
793 2017, **12**, e0179739.

794 10. C. A. Thaiss, H. Shapiro and E. Elinav, Post-dieting weight gain: the role of persistent
795 microbiome changes, *Future microbiology*, 2017, **12**, 555-559.

796 11. M. I. Smith, T. Yatsunenko, M. J. Manary, I. Trehan, R. Mkakosya, J. Cheng, A. L. Kau, S.
797 S. Rich, P. Concannon, J. C. Mychaleckyj, J. Liu, E. Houghton, J. V. Li, E. Holmes, J.
798 Nicholson, D. Knights, L. K. Ursell, R. Knight and J. I. Gordon, Gut microbiomes of
799 Malawian twin pairs discordant for kwashiorkor, *Science*, 2013, **339**, 548-554.

800 12. F. Sommer, J. M. Anderson, R. Bharti, J. Raes and P. Rosenstiel, The resilience of the
801 intestinal microbiota influences health and disease, *Nature reviews. Microbiology*,
802 2017, **15**, 630-638.

803 13. E. G. Zoetendal, A. D. Akkermans and W. M. De Vos, Temperature gradient gel
804 electrophoresis analysis of 16S rRNA from human fecal samples reveals stable and
805 host-specific communities of active bacteria, *Applied and environmental microbiology*,
806 1998, **64**, 3854-3859.

807 14. S. R. Gill, M. Pop, R. T. Deboy, P. B. Eckburg, P. J. Turnbaugh, B. S. Samuel, J. I. Gordon,
808 D. A. Relman, C. M. Fraser-Liggett and K. E. Nelson, Metagenomic analysis of the
809 human distal gut microbiome, *Science*, 2006, **312**, 1355-1359.

810 15. P. J. Turnbaugh, M. Hamady, T. Yatsunenko, B. L. Cantarel, A. Duncan, R. E. Ley, M. L.
811 Sogin, W. J. Jones, B. A. Roe, J. P. Affourtit, M. Egholm, B. Henrissat, A. C. Heath, R.
812 Knight and J. I. Gordon, A core gut microbiome in obese and lean twins, *Nature*, 2009,
813 **457**, 480-484.

16. K. Kurokawa, T. Itoh, T. Kuwahara, K. Oshima, H. Toh, A. Toyoda, H. Takami, H. Morita, V. K. Sharma, T. P. Srivastava, T. D. Taylor, H. Noguchi, H. Mori, Y. Ogura, D. S. Ehrlich, K. Itoh, T. Takagi, Y. Sakaki, T. Hayashi and M. Hattori, Comparative metagenomics revealed commonly enriched gene sets in human gut microbiomes, *DNA research : an international journal for rapid publication of reports on genes and genomes*, 2007, **14**, 169-181.
17. M. Arumugam, J. Raes, E. Pelletier, D. Le Paslier, T. Yamada, D. R. Mende, G. R. Fernandes, J. Tap, T. Bruls, J. M. Batto, M. Bertalan, N. Borruel, F. Casellas, L. Fernandez, L. Gautier, T. Hansen, M. Hattori, T. Hayashi, M. Kleerebezem, K. Kurokawa, M. Leclerc, F. Levenez, C. Manichanh, H. B. Nielsen, T. Nielsen, N. Pons, J. Poulain, J. Qin, T. Sicheritz-Ponten, S. Tims, D. Torrents, E. Ugarte, E. G. Zoetendal, J. Wang, F. Guarner, O. Pedersen, W. M. de Vos, S. Brunak, J. Dore, H. I. T. C. Meta, M. Antolin, F. Artiguenave, H. M. Blottiere, M. Almeida, C. Brechot, C. Cara, C. Chervaux, A. Cultrone, C. Delorme, G. Denariáz, R. Dervyn, K. U. Foerstner, C. Friss, M. van de Guchte, E. Guedon, F. Haimet, W. Huber, J. van Hylckama-Vlieg, A. Jamet, C. Juste, G. Kaci, J. Knol, O. Lakhdari, S. Layec, K. Le Roux, E. Maguin, A. Merieux, R. Melo Minardi, C. M'Rini, J. Muller, R. Oozeer, J. Parkhill, P. Renault, M. Rescigno, N. Sanchez, S. Sunagawa, A. Torrejon, K. Turner, G. Vandemeulebrouck, E. Varela, Y. Winogradsky, G. Zeller, J. Weissenbach, S. D. Ehrlich and P. Bork, Enterotypes of the human gut microbiome, *Nature*, 2011, **473**, 174-180.
18. G. D. Wu, J. Chen, C. Hoffmann, K. Bittinger, Y. Y. Chen, S. A. Keilbaugh, M. Bewtra, D. Knights, W. A. Walters, R. Knight, R. Sinha, E. Gilroy, K. Gupta, R. Baldassano, L. Nessel, H. Li, F. D. Bushman and J. D. Lewis, Linking long-term dietary patterns with gut microbial enterotypes, *Science*, 2011, **334**, 105-108.
19. C. De Filippo, D. Cavalieri, M. Di Paola, M. Ramazzotti, J. B. Poullet, S. Massart, S. Collini, G. Pieraccini and P. Lionetti, Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa, *Proceedings of the National Academy of Sciences of the United States of America*, 2010, **107**, 14691-14696.
20. I. Martinez, J. C. Stegen, M. X. Maldonado-Gomez, A. M. Eren, P. M. Siba, A. R. Greenhill and J. Walter, The gut microbiota of rural papua new guineans: composition, diversity patterns, and ecological processes, *Cell reports*, 2015, **11**, 527-538.
21. L. Mancabelli, C. Milani, G. A. Lugli, F. Turroni, C. Ferrario, D. van Sinderen and M. Ventura, Meta-analysis of the human gut microbiome from urbanized and pre-agricultural populations, *Environmental microbiology*, 2017, **19**, 1379-1390.
22. T. Yatsunenko, F. E. Rey, M. J. Manary, I. Trehan, M. G. Dominguez-Bello, M. Contreras, M. Magris, G. Hidalgo, R. N. Baldassano, A. P. Anokhin, A. C. Heath, B. Warner, J. Reeder, J. Kuczynski, J. G. Caporaso, C. A. Lozupone, C. Lauber, J. C. Clemente, D. Knights, R. Knight and J. I. Gordon, Human gut microbiome viewed across age and geography, *Nature*, 2012, **486**, 222-227.
23. S. Rampelli, S. L. Schnorr, C. Consolandi, S. Turroni, M. Severgnini, C. Peano, P. Brigidi, A. N. Crittenden, A. G. Henry and M. Candela, Metagenome Sequencing of the Hadza Hunter-Gatherer Gut Microbiota, *Current biology : CB*, 2015, **25**, 1682-1693.
24. S. L. Schnorr, M. Candela, S. Rampelli, M. Centanni, C. Consolandi, G. Basaglia, S. Turroni, E. Biagi, C. Peano, M. Severgnini, J. Fiori, R. Gotti, G. De Bellis, D. Luiselli, P. Brigidi, A. Mabulla, F. Marlowe, A. G. Henry and A. N. Crittenden, Gut microbiome of the Hadza hunter-gatherers, *Nature communications*, 2014, **5**, 3654.
25. S. Turroni, J. Fiori, S. Rampelli, S. L. Schnorr, C. Consolandi, M. Barone, E. Biagi, F. Fanelli, M. Mezzullo, A. N. Crittenden, A. G. Henry, P. Brigidi and M. Candela, Fecal metabolome of the Hadza hunter-gatherers: a host-microbiome integrative view, *Scientific reports*, 2016, **6**, 32826.

- 865 26. J. C. Clemente, E. C. Pehrsson, M. J. Blaser, K. Sandhu, Z. Gao, B. Wang, M. Magris, G.
866 Hidalgo, M. Contreras, O. Noya-Alarcon, O. Lander, J. McDonald, M. Cox, J. Walter, P. L.
867 Oh, J. F. Ruiz, S. Rodriguez, N. Shen, S. J. Song, J. Metcalf, R. Knight, G. Dantas and M.
868 G. Dominguez-Bello, The microbiome of uncontacted Amerindians, *Science advances*,
869 2015, **1**.
- 870 27. A. J. Obregon-Tito, R. Y. Tito, J. Metcalf, K. Sankaranarayanan, J. C. Clemente, L. K.
871 Ursell, Z. Zech Xu, W. Van Treuren, R. Knight, P. M. Gaffney, P. Spicer, P. Lawson, L.
872 Marin-Reyes, O. Trujillo-Villarreal, M. Foster, E. Gujia-Poma, L. Troncoso-Corzo, C.
873 Warinner, A. T. Ozga and C. M. Lewis, Subsistence strategies in traditional societies
874 distinguish gut microbiomes, *Nature communications*, 2015, **6**, 6505.
- 875 28. E. R. Morton, J. Lynch, A. Froment, S. Lafosse, E. Heyer, M. Przeworski, R. Blehman
876 and L. Segurel, Variation in Rural African Gut Microbiota Is Strongly Correlated with
877 Colonization by Entamoeba and Subsistence, *PLoS genetics*, 2015, **11**, e1005658.
- 878 29. M. Anwesh, K. V. Kumar, M. Nagarajan, M. P. Chander, C. Kartick and V. Paluru,
879 Elucidating the richness of bacterial groups in the gut of Nicobarese tribal community -
880 Perspective on their lifestyle transition, *Anaerobe*, 2016, **39**, 68-76.
- 881 30. A. Gomez, K. J. Petrzalkova, M. B. Burns, C. J. Yeoman, K. R. Amato, K. Vlckova, D.
882 Modry, A. Todd, C. A. Jost Robinson, M. J. Remis, M. G. Torralba, E. Morton, J. D.
883 Umana, F. Carbonero, H. R. Gaskins, K. E. Nelson, B. A. Wilson, R. M. Stumpf, B. A.
884 White, S. R. Leigh and R. Blehman, Gut Microbiome of Coexisting BaAka Pygmies and
885 Bantu Reflects Gradients of Traditional Subsistence Patterns, *Cell reports*, 2016, **14**,
886 2142-2153.
- 887 31. V. K. Gupta, S. Paul and C. Dutta, Geography, Ethnicity or Subsistence-Specific
888 Variations in Human Microbiome Composition and Diversity, *Frontiers in microbiology*,
889 2017, **8**, 1162.
- 890 32. A. Lia, B. Sundberg, P. Aman, A. S. Sandberg, G. Hallmans and H. Andersson, Substrates
891 available for colonic fermentation from oat, barley and wheat bread diets. A study in
892 ileostomy subjects, *The British journal of nutrition*, 1996, **76**, 797-808.
- 893 33. M. N. Read and A. J. Holmes, Towards an Integrative Understanding of Diet-Host-Gut
894 Microbiome Interactions, *Frontiers in immunology*, 2017, **8**, 538.
- 895 34. D. W. Cockburn and N. M. Koropatkin, Polysaccharide Degradation by the Intestinal
896 Microbiota and Its Influence on Human Health and Disease, *Journal of molecular*
897 *biology*, 2016, **428**, 3230-3252.
- 898 35. A. El Kaoutari, F. Armougom, J. I. Gordon, D. Raoult and B. Henrissat, The abundance
899 and variety of carbohydrate-active enzymes in the human gut microbiota, *Nature*
900 *reviews. Microbiology*, 2013, **11**, 497-504.
- 901 36. A. G. Wexler and A. L. Goodman, An insider's perspective: Bacteroides as a window
902 into the microbiome, *Nature microbiology*, 2017, **2**, 17026.
- 903 37. E. C. Martens, E. C. Lowe, H. Chiang, N. A. Pudlo, M. Wu, N. P. McNulty, D. W. Abbott,
904 B. Henrissat, H. J. Gilbert, D. N. Bolam and J. I. Gordon, Recognition and degradation of
905 plant cell wall polysaccharides by two human gut symbionts, *PLoS biology*, 2011, **9**,
906 e1001221.
- 907 38. F. Turrone, C. Milani, S. Duranti, J. Mahony, D. van Sinderen and M. Ventura, Glycan
908 Utilization and Cross-Feeding Activities by Bifidobacteria, *Trends in microbiology*, 2017,
909 DOI: 10.1016/j.tim.2017.10.001.
- 910 39. M. Ejby, F. Fredslund, J. M. Andersen, A. Vujicic Zagar, J. R. Henriksen, T. L. Andersen,
911 B. Svensson, D. J. Slotboom and M. Abou Hachem, An ATP Binding Cassette
912 Transporter Mediates the Uptake of alpha-(1,6)-Linked Dietary Oligosaccharides in
913 Bifidobacterium and Correlates with Competitive Growth on These Substrates, *The*
914 *Journal of biological chemistry*, 2016, **291**, 20220-20231.
- 915 40. M. O'Connell Motherway, G. F. Fitzgerald, S. Neirynck, S. Ryan, L. Steidler and D. van
916 Sinderen, Characterization of ApuB, an extracellular type II amylopullulanase from

- 917 Bifidobacterium breve UCC2003, *Applied and environmental microbiology*, 2008, **74**,
918 6271-6279.
- 919 41. R. G. LoCascio, P. Desai, D. A. Sela, B. Weimer and D. A. Mills, Broad conservation of
920 milk utilization genes in Bifidobacterium longum subsp. infantis as revealed by
921 comparative genomic hybridization, *Applied and environmental microbiology*, 2010,
922 **76**, 7373-7381.
- 923 42. D. A. Sela and D. A. Mills, Nursing our microbiota: molecular linkages between
924 bifidobacteria and milk oligosaccharides, *Trends in microbiology*, 2010, **18**, 298-307.
- 925 43. S. Parche, J. Amon, I. Jankovic, E. Rezzonico, M. Belet, H. Barutcu, I. Schendel, M. P.
926 Eddy, A. Burkovski, F. Arigoni and F. Titgemeyer, Sugar transport systems of
927 Bifidobacterium longum NCC2705, *Journal of molecular microbiology and*
928 *biotechnology*, 2007, **12**, 9-19.
- 929 44. J. M. Andersen, R. Barrangou, M. Abou Hachem, S. Lahtinen, Y. J. Goh, B. Svensson and
930 T. R. Klaenhammer, Transcriptional and functional analysis of galactooligosaccharide
931 uptake by lacS in Lactobacillus acidophilus, *Proceedings of the National Academy of*
932 *Sciences of the United States of America*, 2011, **108**, 17785-17790.
- 933 45. S. W. Hinz, M. I. Pastink, L. A. van den Broek, J. P. Vincken and A. G. Voragen,
934 Bifidobacterium longum endogalactanase liberates galactotriose from type I galactans,
935 *Applied and environmental microbiology*, 2005, **71**, 5501-5510.
- 936 46. M. O'Connell Motherway, M. Kinsella, G. F. Fitzgerald and D. van Sinderen,
937 Transcriptional and functional characterization of genetic elements involved in galacto-
938 oligosaccharide utilization by Bifidobacterium breve UCC2003, *Microbial*
939 *biotechnology*, 2013, **6**, 67-79.
- 940 47. M. A. Mahowald, F. E. Rey, H. Seedorf, P. J. Turnbaugh, R. S. Fulton, A. Wollam, N.
941 Shah, C. Wang, V. Magrini, R. K. Wilson, B. L. Cantarel, P. M. Coutinho, B. Henrissat, L.
942 W. Crock, A. Russell, N. C. Verberkmoes, R. L. Hettich and J. I. Gordon, Characterizing a
943 model human gut microbiota composed of members of its two dominant bacterial
944 phyla, *Proceedings of the National Academy of Sciences of the United States of*
945 *America*, 2009, **106**, 5859-5864.
- 946 48. A. Riviere, M. Gagnon, S. Weckx, D. Roy and L. De Vuyst, Mutual Cross-Feeding
947 Interactions between Bifidobacterium longum subsp. longum NCC2705 and
948 Eubacterium rectale ATCC 33656 Explain the Bifidogenic and Butyrogenic Effects of
949 Arabinoxylan Oligosaccharides, *Applied and environmental microbiology*, 2015, **81**,
950 7767-7781.
- 951 49. H. Kettle, P. Louis, G. Holtrop, S. H. Duncan and H. J. Flint, Modelling the emergent
952 dynamics and major metabolites of the human colonic microbiota, *Environmental*
953 *microbiology*, 2015, **17**, 1615-1630.
- 954 50. N. Reichardt, S. H. Duncan, P. Young, A. Belenguer, C. McWilliam Leitch, K. P. Scott, H.
955 J. Flint and P. Louis, Phylogenetic distribution of three pathways for propionate
956 production within the human gut microbiota, *The ISME journal*, 2014, **8**, 1323-1335.
- 957 51. P. H. Degnan, M. E. Taga and A. L. Goodman, Vitamin B12 as a modulator of gut
958 microbial ecology, *Cell metabolism*, 2014, **20**, 769-778.
- 959 52. D. J. Morrison and T. Preston, Formation of short chain fatty acids by the gut
960 microbiota and their impact on human metabolism, *Gut microbes*, 2016, **7**, 189-200.
- 961 53. J. R. Sieber, M. J. McInerney and R. P. Gunsalus, Genomic insights into syntrophy: the
962 paradigm for anaerobic metabolic cooperation, *Annual review of microbiology*, 2012,
963 **66**, 429-452.
- 964 54. P. Louis and H. J. Flint, Formation of propionate and butyrate by the human colonic
965 microbiota, *Environmental microbiology*, 2017, **19**, 29-41.
- 966 55. E. A. Smith and G. T. Macfarlane, Enumeration of human colonic bacteria producing
967 phenolic and indolic compounds: effects of pH, carbohydrate availability and retention

- time on dissimilatory aromatic amino acid metabolism, *The Journal of applied bacteriology*, 1996, **81**, 288-302.
56. N. D. Rawlings, M. Waller, A. J. Barrett and A. Bateman, MEROPS: the database of proteolytic enzymes, their substrates and inhibitors, *Nucleic acids research*, 2014, **42**, D503-509.
57. M. Liu, J. R. Bayjanov, B. Renckens, A. Nauta and R. J. Siezen, The proteolytic system of lactic acid bacteria revisited: a genomic comparison, *BMC genomics*, 2010, **11**, 36.
58. K. J. Portune, M. Beaumont, A. M. Davila, D. Tome, F. Blachier and Y. Sanz, Gut microbiota role in dietary protein metabolism and health-related outcomes: The two sides of the coin, *Trends Food Sci. Technol.*, 2016, **57**, 213-232.
59. L. A. David, C. F. Maurice, R. N. Carmody, D. B. Gootenberg, J. E. Button, B. E. Wolfe, A. V. Ling, A. S. Devlin, Y. Varma, M. A. Fischbach, S. B. Biddinger, R. J. Dutton and P. J. Turnbaugh, Diet rapidly and reproducibly alters the human gut microbiome, *Nature*, 2014, **505**, 559-563.
60. C. Feehily and K. A. Karatzas, Role of glutamate metabolism in bacterial responses towards acid and other stresses, *Journal of applied microbiology*, 2013, **114**, 11-24.
61. L. Cervantes-Barragan, J. N. Chai, M. D. Tianero, B. Di Luccia, P. P. Ahern, J. Merriman, V. S. Cortez, M. G. Caparon, M. S. Donia, S. Gilfillan, M. Cella, J. I. Gordon, C. S. Hsieh and M. Colonna, *Lactobacillus reuteri* induces gut intraepithelial CD4+CD8 α alpha α + T cells, *Science*, 2017, **357**, 806-810.
62. F. Fava, R. Gitau, B. A. Griffin, G. R. Gibson, K. M. Tuohy and J. A. Lovegrove, The type and quantity of dietary fat and carbohydrate alter faecal microbiome and short-chain fatty acid excretion in a metabolic syndrome 'at-risk' population, *International journal of obesity*, 2013, **37**, 216-223.
63. R. Caesar, V. Tremaroli, P. Kovatcheva-Datchary, P. D. Cani and F. Backhed, Crosstalk between Gut Microbiota and Dietary Lipids Aggravates WAT Inflammation through TLR Signaling, *Cell metabolism*, 2015, **22**, 658-668.
64. A. Everard, C. Belzer, L. Geurts, J. P. Ouwerkerk, C. Druart, L. B. Bindels, Y. Guiot, M. Derrien, G. G. Muccioli, N. M. Delzenne, W. M. de Vos and P. D. Cani, Cross-talk between Akkermansia muciniphila and intestinal epithelium controls diet-induced obesity, *Proceedings of the National Academy of Sciences of the United States of America*, 2013, **110**, 9066-9071.
65. N. R. Shin, J. C. Lee, H. Y. Lee, M. S. Kim, T. W. Whon, M. S. Lee and J. W. Bae, An increase in the Akkermansia spp. population induced by metformin treatment improves glucose homeostasis in diet-induced obese mice, *Gut*, 2014, **63**, 727-735.
66. O. Ramirez-Perez, V. Cruz-Ramon, P. Chinchilla-Lopez and N. Mendez-Sanchez, The Role of the Gut Microbiota in Bile Acid Metabolism, *Annals of hepatology*, 2017, **16**, 15-20.
67. E. J. Baron, Bilophila wadsworthia: a unique Gram-negative anaerobic rod, *Anaerobe*, 1997, **3**, 83-86.
68. S. M. da Silva, S. S. Venceslau, C. L. Fernandes, F. M. Valente and I. A. Pereira, Hydrogen as an energy source for the human pathogen Bilophila wadsworthia, *Antonie van Leeuwenhoek*, 2008, **93**, 381-390.
69. S. Devkota, Y. Wang, M. W. Musch, V. Leone, H. Fehlner-Peach, A. Nadimpalli, D. A. Antonopoulos, B. Jabri and E. B. Chang, Dietary-fat-induced taurocholic acid promotes pathobiont expansion and colitis in IL10 $^{-/-}$ mice, *Nature*, 2012, **487**, 104-108.
70. C. Druart, L. B. Bindels, R. Schmaltz, A. M. Neyrinck, P. D. Cani, J. Walter, A. E. Ramer-Tait and N. M. Delzenne, Ability of the gut microbiota to produce PUFA-derived bacterial metabolites: Proof of concept in germ-free versus conventionalized mice, *Molecular nutrition & food research*, 2015, **59**, 1603-1613.

- 1018 71. E. Devillard, F. M. McIntosh, S. H. Duncan and R. J. Wallace, Metabolism of linoleic acid
1019 by human gut bacteria: different routes for biosynthesis of conjugated linoleic acid,
1020 *Journal of bacteriology*, 2007, **189**, 2566-2570.
- 1021 72. R. C. Robertson, C. Seira Oriach, K. Murphy, G. M. Moloney, J. F. Cryan, T. G. Dinan, R.
1022 Paul Ross and C. Stanton, Omega-3 polyunsaturated fatty acids critically regulate
1023 behaviour and gut microbiota development in adolescence and adulthood, *Brain,*
1024 *behavior, and immunity*, 2017, **59**, 21-37.
- 1025 73. Y. Y. Lam, C. W. Ha, J. M. Hoffmann, J. Oscarsson, A. Dinudom, T. J. Mather, D. I. Cook,
1026 N. H. Hunt, I. D. Caterson, A. J. Holmes and L. H. Storlien, Effects of dietary fat profile
1027 on gut permeability and microbiota and their relationships with metabolic changes in
1028 mice, *Obesity*, 2015, **23**, 1429-1439.
- 1029 74. S. J. Hulin, S. Singh, M. A. Chapman, A. Allan, M. J. Langman and M. C. Eggo, Sulphide-
1030 induced energy deficiency in colonic cells is prevented by glucose but not by butyrate,
1031 *Alimentary pharmacology & therapeutics*, 2002, **16**, 325-331.
- 1032 75. S. Arranz, J. M. Silvan and F. Saura-Calixto, Nonextractable polyphenols, usually
1033 ignored, are the major part of dietary polyphenols: a study on the Spanish diet,
1034 *Molecular nutrition & food research*, 2010, **54**, 1646-1658.
- 1035 76. R. Barbieri, E. Coppo, A. Marchese, M. Daglia, E. Sobarzo-Sanchez, S. F. Nabavi and S.
1036 M. Nabavi, Phytochemicals for human disease: An update on plant-derived
1037 compounds antibacterial activity, *Microbiological research*, 2017, **196**, 44-68.
- 1038 77. J. C. Espin, A. Gonzalez-Sarrias and F. A. Tomas-Barberan, The gut microbiota: A key
1039 factor in the therapeutic effects of (poly)phenols, *Biochemical pharmacology*, 2017,
1040 **139**, 82-93.
- 1041 78. M. Avila, M. Hidalgo, C. Sanchez-Moreno, C. Pelaez, T. Requena and S. de Pascual-
1042 Teresa, Bioconversion of anthocyanin glycosides by Bifidobacteria and Lactobacillus,
1043 *Food Res. Int.*, 2009, **42**, 1453-1461.
- 1044 79. M. Avila, M. Jaquet, D. Moine, T. Requena, C. Pelaez, F. Arigoni and I. Jankovic,
1045 Physiological and biochemical characterization of the two alpha-L-rhamnosidases of
1046 Lactobacillus plantarum NCC245, *Microbiology*, 2009, **155**, 2739-2749.
- 1047 80. A. Braune and M. Blaut, Bacterial species involved in the conversion of dietary
1048 flavonoids in the human gut, *Gut microbes*, 2016, **7**, 216-234.
- 1049 81. F. Sanchez-Patan, R. Tabasco, M. Monagas, T. Requena, C. Pelaez, M. V. Moreno-
1050 Arribas and B. Bartolome, Capability of Lactobacillus plantarum IFPL935 to catabolize
1051 flavan-3-ol compounds and complex phenolic extracts, *Journal of agricultural and food*
1052 *chemistry*, 2012, **60**, 7142-7151.
- 1053 82. R. Tabasco, F. Sanchez-Patan, M. Monagas, B. Bartolome, M. Victoria Moreno-Arribas,
1054 C. Pelaez and T. Requena, Effect of grape polyphenols on lactic acid bacteria and
1055 bifidobacteria growth: resistance and metabolism, *Food microbiology*, 2011, **28**, 1345-
1056 1352.
- 1057 83. M. V. Selma, D. Beltran, R. Garcia-Villalba, J. C. Espin and F. A. Tomas-Barberan,
1058 Description of urolithin production capacity from ellagic acid of two human intestinal
1059 Gordonibacter species, *Food & function*, 2014, **5**, 1779-1784.
- 1060 84. J. M. Landete, J. Arques, M. Medina, P. Gaya, B. de Las Rivas and R. Munoz,
1061 Bioactivation of Phytoestrogens: Intestinal Bacteria and Health, *Critical reviews in food*
1062 *science and nutrition*, 2016, **56**, 1826-1843.
- 1063 85. K. D. Setchell and C. Clerici, Equol: history, chemistry, and formation, *The Journal of*
1064 *nutrition*, 2010, **140**, 1355S-1362S.
- 1065 86. P. Gaya, A. Peiroten, M. Medina and J. M. Landete, Bifidobacterium adolescentis INIA
1066 P784: The first probiotic bacterium capable of producing enterodiols from lignan
1067 extracts, *J. Funct. Food.*, 2017, **29**, 269-274.
- 1068 87. A. S. Neish and R. M. Jones, Redox signaling mediates symbiosis between the gut
1069 microbiota and the intestine, *Gut microbes*, 2014, **5**, 250-253.

- 1070 88. J. Zemleni, J. R. Galloway and D. B. McCormick, Pharmacokinetics of orally and
1071 intravenously administered riboflavin in healthy humans, *The American journal of*
1072 *clinical nutrition*, 1996, **63**, 54-66.
- 1073 89. R. E. Steinert, M. Sadaghian Sadabad, H. J. Harmsen and P. Weber, The prebiotic
1074 concept and human health: a changing landscape with riboflavin as a novel prebiotic
1075 candidate?, *European journal of clinical nutrition*, 2016, **70**, 1348-1353.
- 1076 90. M. C. Hibberd, M. Wu, D. A. Rodionov, X. Li, J. Cheng, N. W. Griffin, M. J. Barratt, R. J.
1077 Giannone, R. L. Hettich, A. L. Osterman and J. I. Gordon, The effects of micronutrient
1078 deficiencies on bacterial species from the human gut microbiota, *Science translational*
1079 *medicine*, 2017, **9**.
- 1080 91. N. Mach and A. Clark, Micronutrient Deficiencies and the Human Gut Microbiota,
1081 *Trends in microbiology*, 2017, **25**, 607-610.
- 1082 92. B. D. Pachikian, A. M. Neyrinck, L. Deldicque, F. C. De Backer, E. Catry, E. M. Dewulf, F.
1083 M. Sohet, L. B. Bindels, A. Everard, M. Francaux, Y. Guiot, P. D. Cani and N. M.
1084 Delzenne, Changes in intestinal bifidobacteria levels are associated with the
1085 inflammatory response in magnesium-deficient mice, *The Journal of nutrition*, 2010,
1086 **140**, 509-514.
- 1087 93. J. Suez, T. Korem, D. Zeevi, G. Zilberman-Schapira, C. A. Thaiss, O. Maza, D. Israeli, N.
1088 Zmora, S. Gilad, A. Weinberger, Y. Kuperman, A. Harmelin, I. Kolodkin-Gal, H. Shapiro,
1089 Z. Halpern, E. Segal and E. Elinav, Artificial sweeteners induce glucose intolerance by
1090 altering the gut microbiota, *Nature*, 2014, **514**, 181-186.
- 1091 94. P. Spanogiannopoulos, E. N. Bess, R. N. Carmody and P. J. Turnbaugh, The microbial
1092 pharmacists within us: a metagenomic view of xenobiotic metabolism, *Nature reviews.*
1093 *Microbiology*, 2016, **14**, 273-287.
- 1094 95. B. Chassaing, O. Koren, J. K. Goodrich, A. C. Poole, S. Srinivasan, R. E. Ley and A. T.
1095 Gewirtz, Dietary emulsifiers impact the mouse gut microbiota promoting colitis and
1096 metabolic syndrome, *Nature*, 2015, **519**, 92-96.
- 1097 96. S. V. Lynch and O. Pedersen, The human intestinal microbiome in health and disease,
1098 *N. Engl. J. Med.*, 2016, **375**, 2369-2379.
- 1099 97. S. Duranti, C. Ferrario, D. van Sinderen, M. Ventura and F. Turrone, Obesity and
1100 microbiota: an example of an intricate relationship, *Genes & nutrition*, 2017, **12**, 18.
- 1101 98. P. J. Turnbaugh, R. E. Ley, M. A. Mahowald, V. Magrini, E. R. Mardis and J. I. Gordon, An
1102 obesity-associated gut microbiome with increased capacity for energy harvest, *Nature*,
1103 2006, **444**, 1027-1031.
- 1104 99. A. Vrieze, E. Van Nood, F. Holleman, J. Salojarvi, R. S. Kootte, J. F. Bartelsman, G. M.
1105 Dallinga-Thie, M. T. Ackermans, M. J. Serlie, R. Oozeer, M. Derrien, A. Druesne, J. E.
1106 Van Hylckama Vlieg, V. W. Bloks, A. K. Groen, H. G. Heilig, E. G. Zoetendal, E. S. Stroes,
1107 W. M. de Vos, J. B. Hoekstra and M. Nieuwdorp, Transfer of intestinal microbiota from
1108 lean donors increases insulin sensitivity in individuals with metabolic syndrome,
1109 *Gastroenterology*, 2012, **143**, 913-916 e917.
- 1110 100. F. Backhed, J. K. Manchester, C. F. Semenkovich and J. I. Gordon, Mechanisms
1111 underlying the resistance to diet-induced obesity in germ-free mice, *Proceedings of the*
1112 *National Academy of Sciences of the United States of America*, 2007, **104**, 979-984.
- 1113 101. R. Caesar, C. S. Reigstad, H. K. Backhed, C. Reinhardt, M. Ketonen, G. O. Lunden, P. D.
1114 Cani and F. Backhed, Gut-derived lipopolysaccharide augments adipose macrophage
1115 accumulation but is not essential for impaired glucose or insulin tolerance in mice, *Gut*,
1116 2012, **61**, 1701-1707.
- 1117 102. C. K. Fleissner, N. Huebel, M. M. Abd El-Bary, G. Loh, S. Klaus and M. Blaut, Absence of
1118 intestinal microbiota does not protect mice from diet-induced obesity, *The British*
1119 *journal of nutrition*, 2010, **104**, 919-929.
- 1120 103. R. Kubeck, C. Bonet-Ripoll, C. Hoffmann, A. Walker, V. M. Muller, V. L. Schuppel, I.
1121 Lagkouvardos, B. Scholz, K. H. Engel, H. Daniel, P. Schmitt-Kopplin, D. Haller, T. Clavel

- and M. Klingenspor, Dietary fat and gut microbiota interactions determine diet-induced obesity in mice, *Molecular metabolism*, 2016, **5**, 1162-1174.
104. A. Koliada, G. Syzenko, V. Moseiko, L. Budovska, K. Puchkov, V. Perederiy, Y. Gavalko, A. Dorofeyev, M. Romanenko, S. Tkach, L. Sineok, O. Lushchak and A. Vaiserman, Association between body mass index and Firmicutes/Bacteroidetes ratio in an adult Ukrainian population, *BMC microbiology*, 2017, **17**, 120.
105. S. Tims, C. Derom, D. M. Jonkers, R. Vlietinck, W. H. Saris, M. Kleerebezem, W. M. de Vos and E. G. Zoetendal, Microbiota conservation and BMI signatures in adult monozygotic twins, *The ISME journal*, 2013, **7**, 707-717.
106. P. J. Turnbaugh and J. I. Gordon, The core gut microbiome, energy balance and obesity, *The Journal of physiology*, 2009, **587**, 4153-4158.
107. J. K. Goodrich, J. L. Waters, A. C. Poole, J. L. Sutter, O. Koren, R. Blekhman, M. Beaumont, W. Van Treuren, R. Knight, J. T. Bell, T. D. Spector, A. G. Clark and R. E. Ley, Human genetics shape the gut microbiome, *Cell*, 2014, **159**, 789-799.
108. H. Zhang, J. K. DiBaise, A. Zuccolo, D. Kudrna, M. Braidotti, Y. Yu, P. Parameswaran, M. D. Crowell, R. Wing, B. E. Rittmann and R. Krajmalnik-Brown, Human gut microbiota in obesity and after gastric bypass, *Proceedings of the National Academy of Sciences of the United States of America*, 2009, **106**, 2365-2370.
109. M. Million, M. Maraninchi, M. Henry, F. Armougom, H. Richet, P. Carrieri, R. Valero, D. Raccach, B. Vialettes and D. Raoult, Obesity-associated gut microbiota is enriched in *Lactobacillus reuteri* and depleted in *Bifidobacterium animalis* and *Methanobrevibacter smithii*, *International journal of obesity*, 2012, **36**, 817-825.
110. M. M. Rodriguez, D. Perez, F. J. Chaves, E. Esteve, P. Marin-Garcia, G. Xifra, J. Vendrell, M. Jove, R. Pamplona, W. Ricart, M. Portero-Otin, M. R. Chacon and J. M. F. Real, Obesity changes the human gut mycobion (vol 5, 14600, 2015), *Scientific reports*, 2016, **6**.
111. V. Tremaroli and F. Backhed, Functional interactions between the gut microbiota and host metabolism, *Nature*, 2012, **489**, 242-249.
112. G. den Besten, A. Bleeker, A. Gerding, K. van Eunen, R. Havinga, T. H. van Dijk, M. H. Oosterveer, J. W. Jonker, A. K. Groen, D. J. Reijngoud and B. M. Bakker, Short-Chain Fatty Acids Protect Against High-Fat Diet-Induced Obesity via a PPARgamma-Dependent Switch From Lipogenesis to Fat Oxidation, *Diabetes*, 2015, **64**, 2398-2408.
113. F. H. Karlsson, V. Tremaroli, I. Nookaew, G. Bergstrom, C. J. Behre, B. Fagerberg, J. Nielsen and F. Backhed, Gut metagenome in European women with normal, impaired and diabetic glucose control, *Nature*, 2013, **498**, 99-103.
114. S. Rabot, M. Membrez, F. Blancher, B. Berger, D. Moine, L. Krause, R. Bibiloni, A. Bruneau, P. Gerard, J. Siddharth, C. L. Lauber and C. J. Chou, High fat diet drives obesity regardless the composition of gut microbiota in mice, *Scientific reports*, 2016, **6**, 32484.
115. A. Woting and M. Blaut, The Intestinal Microbiota in Metabolic Disease, *Nutrients*, 2016, **8**, 202.
116. R. J. Perry, L. Peng, N. A. Barry, G. W. Cline, D. Zhang, R. L. Cardone, K. F. Petersen, R. G. Kibbey, A. L. Goodman and G. I. Shulman, Acetate mediates a microbiome-brain-beta-cell axis to promote metabolic syndrome, *Nature*, 2016, **534**, 213-217.
117. W. H. Tang, Z. Wang, D. J. Kennedy, Y. Wu, J. A. Buffa, B. Agatista-Boyle, X. S. Li, B. S. Levison and S. L. Hazen, Gut microbiota-dependent trimethylamine N-oxide (TMAO) pathway contributes to both development of renal insufficiency and mortality risk in chronic kidney disease, *Circulation research*, 2015, **116**, 448-455.
118. Z. Wang, E. Klipfell, B. J. Bennett, R. Koeth, B. S. Levison, B. Dugar, A. E. Feldstein, E. B. Britt, X. Fu, Y. M. Chung, Y. Wu, P. Schauer, J. D. Smith, H. Allayee, W. H. Tang, J. A. DiDonato, A. J. Lusis and S. L. Hazen, Gut flora metabolism of phosphatidylcholine promotes cardiovascular disease, *Nature*, 2011, **472**, 57-63.

- 1174 119. R. A. Koeth, Z. Wang, B. S. Levison, J. A. Buffa, E. Org, B. T. Sheehy, E. B. Britt, X. Fu, Y.
1175 Wu, L. Li, J. D. Smith, J. A. DiDonato, J. Chen, H. Li, G. D. Wu, J. D. Lewis, M. Warrier, J.
1176 M. Brown, R. M. Krauss, W. H. Tang, F. D. Bushman, A. J. Lusis and S. L. Hazen,
1177 Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes
1178 atherosclerosis, *Nature medicine*, 2013, **19**, 576-585.
- 1179 120. H. Velly, R. A. Britton and G. A. Preidis, Mechanisms of cross-talk between the diet, the
1180 intestinal microbiome, and the undernourished host, *Gut microbes*, 2017, **8**, 98-112.
- 1181 121. M. Tidjani Alou, M. Million, S. I. Traore, D. Mouelhi, S. Khelaifia, D. Bachar, A. Caputo, J.
1182 Delerce, S. Brah, D. Alhousseini, C. Sokhna, C. Robert, B. A. Diallo, A. Diallo, P. Parola,
1183 M. Golden, J. C. Lagier and D. Raoult, Gut Bacteria Missing in Severe Acute
1184 Malnutrition, Can We Identify Potential Probiotics by Culturomics?, *Frontiers in*
1185 *microbiology*, 2017, **8**, 899.
- 1186 122. L. V. Blanton, M. J. Barratt, M. R. Charbonneau, T. Ahmed and J. I. Gordon, Childhood
1187 undernutrition, the gut microbiota, and microbiota-directed therapeutics, *Science*,
1188 2016, **352**, 1533.
- 1189 123. I. Mack, U. Cuntz, C. Gramer, S. Niedermaier, C. Pohl, A. Schwiertz, K. Zimmermann, S.
1190 Zipfel, P. Enck and J. Penders, Weight gain in anorexia nervosa does not ameliorate the
1191 faecal microbiota, branched chain fatty acid profiles, and gastrointestinal complaints,
1192 *Scientific reports*, 2016, **6**, 26752.
- 1193 124. K. T. Dolan and E. B. Chang, Diet, gut microbes, and the pathogenesis of inflammatory
1194 bowel diseases, *Molecular nutrition & food research*, 2017, **61**.
- 1195 125. H. Nagao-Kitamoto, A. B. Shreiner, M. G. Gilliland, 3rd, S. Kitamoto, C. Ishii, A.
1196 Hirayama, P. Kuffa, M. El-Zaatari, H. Grasberger, A. M. Seekatz, P. D. Higgins, V. B.
1197 Young, S. Fukuda, J. Y. Kao and N. Kamada, Functional Characterization of
1198 Inflammatory Bowel Disease-Associated Gut Dysbiosis in Gnotobiotic Mice, *Cellular*
1199 *and molecular gastroenterology and hepatology*, 2016, **2**, 468-481.
- 1200 126. H. Sokol, V. Leducq, H. Aschard, H. P. Pham, S. Jegou, C. Landman, D. Cohen, G. Liguori,
1201 A. Bourrier, I. Nion-Larmurier, J. Cosnes, P. Seksik, P. Langella, D. Skurnik, M. L. Richard
1202 and L. Beaugerie, Fungal microbiota dysbiosis in IBD, *Gut*, 2017, **66**, 1039-1048.
- 1203 127. C. Manichanh, N. Borruel, F. Casellas and F. Guarner, The gut microbiota in IBD, *Nature*
1204 *reviews. Gastroenterology & hepatology*, 2012, **9**, 599-608.
- 1205 128. A. Manson McGuire, K. Cochrane, A. D. Griggs, B. J. Haas, T. Abeel, Q. Zeng, J. B. Nice,
1206 H. MacDonald, B. W. Birren, B. W. Berger, E. Allen-Vercoe and A. M. Earl, Evolution of
1207 invasion in a diverse set of *Fusobacterium* species, *mBio*, 2014, **5**, e01864.
- 1208 129. X. C. Morgan, T. L. Tickle, H. Sokol, D. Gevers, K. L. Devaney, D. V. Ward, J. A. Reyes, S.
1209 A. Shah, N. LeLeiko, S. B. Snapper, A. Bousvaros, J. Korzenik, B. E. Sands, R. J. Xavier
1210 and C. Huttenhower, Dysfunction of the intestinal microbiome in inflammatory bowel
1211 disease and treatment, *Genome biology*, 2012, **13**, R79.
- 1212 130. S. Greenblum, P. J. Turnbaugh and E. Borenstein, Metagenomic systems biology of the
1213 human gut microbiome reveals topological shifts associated with obesity and
1214 inflammatory bowel disease, *Proceedings of the National Academy of Sciences of the*
1215 *United States of America*, 2012, **109**, 594-599.
- 1216 131. W. S. Nanayakkara, P. M. Skidmore, L. O'Brien, T. J. Wilkinson and R. B. Gearry, Efficacy
1217 of the low FODMAP diet for treating irritable bowel syndrome: the evidence to date,
1218 *Clinical and experimental gastroenterology*, 2016, **9**, 131-142.
- 1219 132. N. Haskey and D. L. Gibson, An Examination of Diet for the Maintenance of Remission
1220 in Inflammatory Bowel Disease, *Nutrients*, 2017, **9**.
- 1221 133. D. Lee, L. Albenberg, C. Compher, R. Baldassano, D. Piccoli, J. D. Lewis and G. D. Wu,
1222 Diet in the pathogenesis and treatment of inflammatory bowel diseases,
1223 *Gastroenterology*, 2015, **148**, 1087-1106.
- 1224 134. V. Dimitrov and J. H. White, Vitamin D signaling in intestinal innate immunity and
1225 homeostasis, *Molecular and cellular endocrinology*, 2017, **453**, 68-78.

- 1226 135. J. H. Ooi, Y. Li, C. J. Rogers and M. T. Cantorna, Vitamin D regulates the gut microbiome
1227 and protects mice from dextran sodium sulfate-induced colitis, *The Journal of*
1228 *nutrition*, 2013, **143**, 1679-1686.
- 1229 136. P. Jantchou, F. Clavel-Chapelon, A. Racine, M. Kvaskoff, F. Carbonnel and M. C.
1230 Boutron-Ruault, High residential sun exposure is associated with a low risk of incident
1231 Crohn's disease in the prospective E3N cohort, *Inflammatory bowel diseases*, 2014, **20**,
1232 75-81.
- 1233 137. B. N. Limketkai, T. M. Bayless, S. R. Brant and S. M. Hutfless, Lower regional and
1234 temporal ultraviolet exposure is associated with increased rates and severity of
1235 inflammatory bowel disease hospitalisation, *Alimentary pharmacology & therapeutics*,
1236 2014, **40**, 508-517.
- 1237 138. D. R. Linden, Hydrogen sulfide signaling in the gastrointestinal tract, *Antioxidants &*
1238 *redox signaling*, 2014, **20**, 818-830.
- 1239 139. J. P. Motta, K. L. Flannigan, T. A. Agbor, J. K. Beatty, R. W. Blackler, M. L. Workentine,
1240 G. J. Da Silva, R. Wang, A. G. Buret and J. L. Wallace, Hydrogen sulfide protects from
1241 colitis and restores intestinal microbiota biofilm and mucus production, *Inflammatory*
1242 *bowel diseases*, 2015, **21**, 1006-1017.
- 1243 140. D. D. Alexander, D. L. Weed, P. E. Miller and M. A. Mohamed, Red Meat and Colorectal
1244 Cancer: A Quantitative Update on the State of the Epidemiologic Science, *Journal of*
1245 *the American College of Nutrition*, 2015, **34**, 521-543.
- 1246 141. A. Vulcan, J. Manjer, U. Ericson and B. Ohlsson, Intake of different types of red meat,
1247 poultry, and fish and incident colorectal cancer in women and men: results from the
1248 Malmo Diet and Cancer Study, *Food & nutrition research*, 2017, **61**, 1341810.
- 1249 142. B. Flemer, D. B. Lynch, J. M. Brown, I. B. Jeffery, F. J. Ryan, M. J. Claesson, M.
1250 O'Riordain, F. Shanahan and P. W. O'Toole, Tumour-associated and non-tumour-
1251 associated microbiota in colorectal cancer, *Gut*, 2017, **66**, 633-643.
- 1252 143. L. Mira-Pascual, R. Cabrera-Rubio, S. Ocon, P. Costales, A. Parra, A. Suarez, F. Moris, L.
1253 Rodrigo, A. Mira and M. C. Collado, Microbial mucosal colonic shifts associated with
1254 the development of colorectal cancer reveal the presence of different bacterial and
1255 archaeal biomarkers, *Journal of gastroenterology*, 2015, **50**, 167-179.
- 1256 144. W. Chen, F. Liu, Z. Ling, X. Tong and C. Xiang, Human intestinal lumen and mucosa-
1257 associated microbiota in patients with colorectal cancer, *PloS one*, 2012, **7**, e39743.
- 1258 145. S. J. Bultman, Interplay between diet, gut microbiota, epigenetic events, and colorectal
1259 cancer, *Molecular nutrition & food research*, 2017, **61**.
- 1260 146. A. Boleij, E. M. Hechenbleikner, A. C. Goodwin, R. Badani, E. M. Stein, M. G. Lazarev, B.
1261 Ellis, K. C. Carroll, E. Albesiano, E. C. Wick, E. A. Platz, D. M. Pardoll and C. L. Sears, The
1262 *Bacteroides fragilis* toxin gene is prevalent in the colon mucosa of colorectal cancer
1263 patients, *Clinical infectious diseases : an official publication of the Infectious Diseases*
1264 *Society of America*, 2015, **60**, 208-215.
- 1265 147. J. Ou, F. Carbonero, E. G. Zoetendal, J. P. DeLany, M. Wang, K. Newton, H. R. Gaskins
1266 and S. J. O'Keefe, Diet, microbiota, and microbial metabolites in colon cancer risk in
1267 rural Africans and African Americans, *The American journal of clinical nutrition*, 2013,
1268 **98**, 111-120.
- 1269 148. M. Medani, D. Collins, N. G. Docherty, A. W. Baird, P. R. O'Connell and D. C. Winter,
1270 Emerging role of hydrogen sulfide in colonic physiology and pathophysiology,
1271 *Inflammatory bowel diseases*, 2011, **17**, 1620-1625.
- 1272 149. R. M. Gadaleta, O. Garcia-Irigoyen and A. Moschetta, Bile acids and colon cancer: Is
1273 FXR the solution of the conundrum?, *Molecular aspects of medicine*, 2017, **56**, 66-74.
- 1274 150. F. Zhang, Y. Zhang, W. Zhao, K. Deng, Z. Wang, C. Yang, L. Ma, M. S. Openkova, Y. Hou
1275 and K. Li, Metabolomics for biomarker discovery in the diagnosis, prognosis, survival
1276 and recurrence of colorectal cancer: a systematic review, *Oncotarget*, 2017, **8**, 35460-
1277 35472.

1278 151. K. Lawrence and J. Hyde, Microbiome restoration diet improves digestion, cognition
1279 and physical and emotional wellbeing, *PloS one*, 2017, **12**, e0179017.
1280 152. H. M. Staudacher and K. Whelan, The low FODMAP diet: recent advances in
1281 understanding its mechanisms and efficacy in IBS, *Gut*, 2017, **66**, 1517-1527.
1282 153. P. Hill, J. G. Muir and P. R. Gibson, Controversies and Recent Developments of the Low-
1283 FODMAP Diet, *Gastroenterology & hepatology*, 2017, **13**, 36-45.
1284 154. C. I. Daien, G. V. Pinget, J. K. Tan and L. Macia, Detrimental Impact of Microbiota-
1285 Accessible Carbohydrate-Deprived Diet on Gut and Immune Homeostasis: An
1286 Overview, *Frontiers in immunology*, 2017, **8**, 548.
1287 155. C. Druart, M. Alligier, N. Salazar, A. M. Neyrinck and N. M. Delzenne, Modulation of the
1288 gut microbiota by nutrients with prebiotic and probiotic properties, *Advances in*
1289 *nutrition*, 2014, **5**, 624S-633S.
1290 156. J. Y. Yoo and S. S. Kim, Probiotics and Prebiotics: Present Status and Future
1291 Perspectives on Metabolic Disorders, *Nutrients*, 2016, **8**.
1292 157. H. Plovier, A. Everard, C. Druart, C. Depommier, M. Van Hul, L. Geurts, J. Chilloux, N.
1293 Ottman, T. Duparc, L. Lichtenstein, A. Myridakis, N. M. Delzenne, J. Klievink, A.
1294 Bhattacharjee, K. C. van der Ark, S. Aalvink, L. O. Martinez, M. E. Dumas, D. Maiter, A.
1295 Loumaye, M. P. Hermans, J. P. Thissen, C. Belzer, W. M. de Vos and P. D. Cani, A
1296 purified membrane protein from Akkermansia muciniphila or the pasteurized
1297 bacterium improves metabolism in obese and diabetic mice, *Nature medicine*, 2017,
1298 **23**, 107-113.
1299 158. L. Crovesy, M. Ostrowski, D. Ferreira, E. L. Rosado and M. Soares-Mota, Effect of
1300 Lactobacillus on body weight and body fat in overweight subjects: a systematic review
1301 of randomized controlled clinical trials, *International journal of obesity*, 2017, **41**, 1607-
1302 1614.
1303 159. E. Nova, F. Perez de Heredia, S. Gomez-Martinez and A. Marcos, The Role of Probiotics
1304 on the Microbiota: Effect on Obesity, *Nutrition in clinical practice : official publication*
1305 *of the American Society for Parenteral and Enteral Nutrition*, 2016, **31**, 387-400.
1306 160. E. Patterson, R. Wall, S. Lisai, R. P. Ross, T. G. Dinan, J. F. Cryan, G. F. Fitzgerald, S.
1307 Banni, E. M. Quigley, F. Shanahan and C. Stanton, Bifidobacterium breve with alpha-
1308 linolenic acid alters the composition, distribution and transcription factor activity
1309 associated with metabolism and absorption of fat, *Scientific reports*, 2017, **7**, 43300.
1310 161. L. Geurts, A. M. Neyrinck, N. M. Delzenne, C. Knauf and P. D. Cani, Gut microbiota
1311 controls adipose tissue expansion, gut barrier and glucose metabolism: novel insights
1312 into molecular targets and interventions using prebiotics, *Beneficial microbes*, 2014, **5**,
1313 3-17.
1314 162. L. B. Bindels, R. R. Segura Munoz, J. C. Gomes-Neto, V. Mutemberezi, I. Martinez, N.
1315 Salazar, E. A. Cody, M. I. Quintero-Villegas, H. Kittana, C. G. de Los Reyes-Gavilan, R. J.
1316 Schmaltz, G. G. Muccioli, J. Walter and A. E. Ramer-Tait, Resistant starch can improve
1317 insulin sensitivity independently of the gut microbiota, *Microbiome*, 2017, **5**, 12.
1318 163. J. Zhou, R. J. Martin, A. M. Raggio, L. Shen, K. McCutcheon and M. J. Keenan, The
1319 importance of GLP-1 and PYY in resistant starch's effect on body fat in mice, *Molecular*
1320 *nutrition & food research*, 2015, **59**, 1000-1003.
1321 164. C. A. Thaïss, S. I. Tav, D. Rothschild, M. T. M. Eijer, M. Levy, C. Moresi, L. Dohnalova, S.
1322 Braverman, S. Rozin, S. Malitsky, M. Dori-Bachash, Y. Kuperman, I. Biton, A. Gertler, A.
1323 Harmelin, H. Shapiro, Z. Halpern, A. Aharoni, E. Segal and E. Elinav, Persistent
1324 microbiome alterations modulate the rate of post-dieting weight regain, *Nature*, 2016,
1325 **540**, 544-+.
1326 165. Y. Y. Lam, S. Maguire, T. Palacios and I. D. Caterson, Are the Gut Bacteria Telling Us to
1327 Eat or Not to Eat? Reviewing the Role of Gut Microbiota in the Etiology, Disease
1328 Progression and Treatment of Eating Disorders, *Nutrients*, 2017, **9**.

- 1329 166. D. V. Seidel, M. A. Azcarate-Peril, R. S. Chapkin and N. D. Turner, Shaping functional gut
1330 microbiota using dietary bioactives to reduce colon cancer risk, *Seminars in cancer*
1331 *biology*, 2017, **46**, 191-204.
- 1332 167. T. Van Raay and E. Allen-Vercoe, Microbial Interactions and Interventions in Colorectal
1333 Cancer, *Microbiology spectrum*, 2017, **5**.
- 1334 168. I. B. Jeffery, M. J. Claesson, P. W. O'Toole and F. Shanahan, Categorization of the gut
1335 microbiota: enterotypes or gradients?, *Nature reviews. Microbiology*, 2012, **10**, 591-
1336 592.
- 1337 169. M. Rajilic-Stojanovic, H. Heilig, S. Tims, E. G. Zoetendal and W. M. de Vos, Long-term
1338 monitoring of the human intestinal microbiota composition, *Environmental*
1339 *microbiology*, 2013, **15**, 1146-1159.
- 1340 170. P. Y. Lee, S. F. Chin, H. M. Neoh and R. Jamal, Metaproteomic analysis of human gut
1341 microbiota: where are we heading?, *Journal of biomedical science*, 2017, **24**, 36.
- 1342 171. L. Putignani and B. Dallapiccola, Foodomics as part of the host-microbiota-exposome
1343 interplay, *Journal of proteomics*, 2016, **147**, 3-20.

1344

1345

Diet and microbiota linked in health and disease