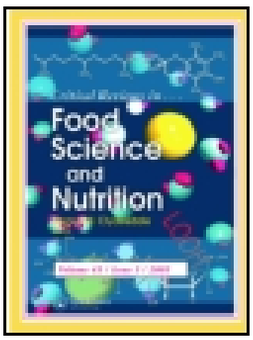

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REVIEW

Roles of intestinal *bacteroides* in human health and diseases

Chen Wang[a,b], Jianxin Zhao[a,b], Hao Zhang[a,b,c,d,e], Yuan-Kun Lee[h], Qixiao Zhai[a,b,f], and Wei Chen[a,b,c,g]

[a]State Key Laboratory of Food Science and Technology, Jiangnan University, Wuxi, P.R. China; [b]School of Food Science and Technology, Jiangnan University, Wuxi, China; [c]National Engineering Research Center for Functional Food, Jiangnan University, Wuxi, China; [d]Research Institute, Wuxi Translational Medicine Research Center and Jiangsu Translational Medicine, Wuxi, China; [e](Yangzhou) Institute of Food Biotechnology, Jiangnan University, Yangzhou, China; [f]International Joint Research Laboratory for Probiotics, Jiangnan University, Wuxi, China; [g]Beijing Innovation Centre of Food Nutrition and Human Health, Beijing Technology and Business University (BTBU), Beijing, P.R. China; [h]Department of Microbiology & Immunology, National University of Singapore, Singapore, Singapore

ABSTRACT

Bacteroides, an abundant genus in the intestines of mammals, has been recently considered as the next generation probiotics (NGP) candidate due to its potential role in promoting host health. However, the role of *Bacteroides* in the development of intestinal dysfunctions such as diarrhea, inflammatory bowel disease, and colorectal cancer should not be overlooked. In the present study, we focused on nine most widely occurred and abundant *Bacteroides* species and discussed their roles in host immunity, glucose and lipid metabolism and the prevention or induction of diseases. Besides, we also discussed the current methods used in the safety evaluation of *Bacteroides* species and key opinions about the concerns of these strains for the future use.

KEYWORDS

Bacteroides; mechanism; opportunistic pathogenic anaerobe; probiotic candidate

Introduction

Bacteroides is a genus of non-spore-forming, bile-resistant, motile or nonmotile, gram-negative, strictly anaerobic bacteria. *Bacteroides fragilis* (*B. fragilis*) was the first *Bacteroides* sp. to be described in 1898 (Veillon and Zuber 1898). After that, the *Bacteroides* genus was included in the Approved Lists of Bacterial Names published online by the International Journal of Systematic and Evolutionary Microbiology in 1980 (Skerman, Mcgowan, and Sneath 1980a). In previous studies, *Bacteroides* species have been isolated from intestines of different hosts including humans (Veillon and Zuber 1898), mice (Miyamoto and Itoh 2000), chickens (Lan et al. 2006; Irisawa et al. 2016) and insects (Sakamoto and Ohkuma 2013). To date, 56 species of *Bacteroides* have been isolated and identified, 30 of which are inhabitants of the human intestine (Table 1), suggesting that this genus is relatively complex and includes diverse species (Ley et al. 2008). According to the National Center for Biotechnology Information, the genus *Bacteroides* is classified under the family Bacteroidaceae, order Bacteroidales, class Bacteroidia, phylum Bacteroidetes and domain Bacteria.

Many studies showed that *Bacteroides* is a predominant genus in the human intestine, accounting for almost up to 25% of the total intestinal microbiota (Ochoa-Repáraz et al. 2010). They colonized the host intestinal niche for an extremely long time and co-evolved with host to establish a stable mutual symbiosis relationship (Faith et al. 2013). All of these characteristics contribute to their unique physiological characteristics: (i) Regulation of the intestinal microenvironment (Wexler and Goodman 2017). Typically, some species of *Bacteroides* could regulate redox levels in the intestine (Baughn and Malamy 2004; Meehan et al. 2012; Rocha and Smith 2013) to create a favorable environment for its growth and transmission to new hosts (Wexler and Goodman 2017). (ii) Carbohydrate metabolism. The Carbohydrate-Active Enzymes (CAZy) database shows 34,218 polysaccharide utilization locus (PUL) predictions in 1,116 Bacteroidetes species. The CAZymes encoded by these PULs endowed them with extremely wide carbohydrate utilization abilities ranging from diet-derived complex polysaccharides to host-derived mucin glycans and thus provide a competitive advantage by orchestrating the breakdown of complex glycans. (iii) Strong adaptability in host environment. *B. fragilis* contains many enzymes, including a bile salt hydrolase (Stellwag and Hylemon 1976; Corzo and Gilliland 1999), which is involved in the biotransformation between conjugated and deconjugated bile salts. In addition, some *Bacteroides* species can evade the host immune response by modulating their surface polysaccharides (Krinos et al. 2001). (iv) Secreting metabolites, such as short chain fatty acids. Some *Bacteroides* species, especially those that inhabit the human gut, can produce acetate, propionate, and butyrate as the main end-products of sugar fermentation (Holdeman and Moore 1974; Salyers, Gherardini, and O'Brien 1981; Fu et al. 2019). Notably, acetate can prevent the transport of toxins between the gut lumen and blood (Fukuda et al. 2011), and propionate can prevent colon tumor formation in humans by inducing the apoptosis of

CONTACT Qixiao Zhai zhaiqixiao@sina.com State Key Laboratory of Food Science and Technology, Jiangnan University, Wuxi, Jiangsu 214122, P.R. China.

Table 1. Basic information on *Bacteroides* species and related reports.

	Species	Type strain: No.	Type strain: Source	Type strain: Genome accession no.	The number of genomes	Median: total length (Mb)	Median: protein count	Median: GC%	The number of searchable reports based on different search engines: Google	The number of searchable reports based on different search engines: Web of science	The number of searchable reports based on different search engines: PubMed	Reference
1	A. *acidifaciens*	A40 = JCM 10556	mice cecum	BAIW01000001.1	7	5.1	3887	43.3	675	49	28	Miyamoto and Itoh 2000
2	*B. barnesiae*	BL2 = DSM 18169 = JCM 13652	chicken cecum	NZ_KB894643.1	3	3.6	2723	46.8	105	3	3	Lan et al. 2006
3	*B. bouchesdurhonensis*	Marseille-P2653T = CSUR P2653	human gut	FTLV00000000.1	1	5.3	4251	39.8	8	0	0	Ndongo et al. 2019
4	*B. caccae*	ATCC 43185 = CCUG 38735 = CIP 104201 = JCM 9498 = NCTC 13051 = VPI 3452A	human feces	NZ_CP022412.2	19	5.3	4023	42.6	2690	112	63	Johnson, Moore, and Moore 1986
5	A. *caecicola*	C13EG70 = LIPI12-4-Ck732 = JSAT12-4-Ck732 = InaCC B449 = NBRC 110958	chicken cecum	Not found	–	–	–	–	18	1	1	Irisawa et al. 2016
6	*B. caecigallinarum*	C13EG111 = LIPI12-4-Ck773 = JSAT12-4-Ck773 = InaCC B455 = NBRC 110959.	chicken cecum	Not found	–	–	–	–	9	1	1	Saputra et al. 2015
7	A. *caecimuris*	I48 = DSM 26085 = KCTC 15547	mouse intestinal	NZ_CP015401.2	3	4.8	3799	42.6	47	1	1	Lagkouvardos et al. 2016
8	*B. cellulosilyticus*	CRE21 = CCUG 44979 = DSM 14838 = JCM 15632	human gut	NZ_EQ973490.1	12	7.0	5190	42.75	641	21	11	Robert et al. 2007
9	*B. clarus*	YIT 12056 = DSM 22519 = JCM 16067	human feces	NZ_GL882599.1	7	4.2	3354	45.4	258	5	2	Watanabe et al. 2010
10	*B. coagulans*	ATCC 29798 = CCUG 48292 = DSM 20705 = JCM 12528 = LMG 8206	human feces	NZ_QEKV01000001.1	1	1.8	1595	35.6	2480	15	7	Eggerth and Gagnon 1933
11	A. *coprocola*	M16 = DSM 17136 = JCM 12979	human feces	NZ_DS981457.1	2	3.9	3155	41.35	343	9	7	Kitahara et al. 2005
12	*B. coprophilus*	CB42 = DSM 18228 = JCM 13818	human feces	NZ_EQ973643.1	6	3.9	2670	45.7	400	11	2	Hayashi et al. 2007
13	A. *coprosuis*	PC139 = CCUG 50528 = DSM 18011 = JCM 13475 = NRRL B-41113	swine-manure storage pits	NZ_CM001167.1	1	3.0	2391	35	154	5	5	Whitehead et al. 2005
14	*B. cutis*	Marseille-P4118T = CSUR P4118	human skin	OEST00000000.1	1	3.9	3085	41.4	1560	4	4	Belkacemi et al. 2018
15	*B. dorei*	175 = DSM 17855 = JCM 13471	human feces	NZ_DS995537.1	25	5.6	4470	41.9	1030	59	39	Bakir et al. 2006c
16	*B. eggerthii*	ATCC 27754 = CCUG 9559 = CIP 104285 =DSM 20697 = JCM 12986 = NCTC 11155	human feces	NZ_DS995509.1	13	4.2	3376	44.7	6760	77	43	Holdeman and Moore 1974
17	*B. faecalis*	DMS 107828; KCTC 15687; KGMB02408	human feces	BHWB01000000	1	–	–	39.5	1	1	1	Yu et al. 2019
18	*B. faecichinchillae*	ST37 = CCUG 60873 = JCM 17102	chinchilla lanigera feces.	NZ_BAKK01000001.1	3	4.8	3645	38.7	45	2	2	Kitahara et al. 2012
19	*B. faecis*	MAJ27 = JCM 16478 = KCTC 5823	human feces	NZ_AGDG01000027.1	6	6.0	4548	42.4	15900	16	10	Kim, Roh, and Bae 2010
20	*B. finegoldii*	19 =DSM 17565 = JCM 13345	human feces	NZ_GG688317.1	5	4.9	3811	42.5	679	30	12	Bakir et al. 2006a
21	*B. fluxus*	YIT 12057 = DSM 22534 = JCM 16101	human feces	NZ_GL882689.1	1	4.3	3439	45.6	113	1	1	Watanabe et al. 2010
22	*B. fragilis*	ATCC 25285 = CCUG 4856 = CIP 77.16 =DSM 2151 = JCM 11019 = LMG 10263 = NCTC 9343	human feces	NC_003228.3	166	5.3	4432	43.4	70400	8509	5559	Veillon and Zuber 1898
23	*B. galacturonicus*	N6 = ATCC 43244 = DSM 3978	human intestinal tract	Not found	–	–	–	–	158	4	3	Jensen and Canale-Parola 1986
24	*B. gallinaceum*	C13EG186 = LIPI12-4-Ck844 = JSAT12-4-Ck884 = InaCC B451 = NBRC 110963	chicken cecum	Not found	–	–	–	–	67	1	1	Irisawa et al. 2016
25	*B. gallinarum*	C35 =DSM 18171 = JCM 13658	chicken cecum	NZ_KB894115.1	2	4.9	3646	47.75	2960	23	5	Lan et al. 2006
26	*B. graminisolvens*	XDT-1 = DSM 19988 = JCM 15093	methanogenic reactor treating cattle waste	NZ_ATZI01000001.1	6	3.0	2510	41.65	150	6	4	Nishiyama et al. 2009
27	*B. helcogenes*	P 36-108 = ATCC 35417 = CCUG 15421 = DSM 20613 = JCM 6297	abscesses and feces of pigs	CP002352.1	1	4.0	3187	44.7	327	9	5	Benno, Watabe, and Mitsuoka 1983
28	*B. ihuae*	Marseille-P2824T = CSUR P2824	human respiratory microbiome	FNVX00000000.1	1	4.1	3202	39.7	14	2	2	Fonkou et al. 2017
29	*B. intestinalis*	341 = DSM 17393 = JCM 13265	human feces	ABJL00000000.2	17	6.0	4522	42.6	5030	94	45	Bakir et al. 2006b
30	*B. koreensis*	YS-aM39 = KCTC 15520 = JCM 31393	human feces	Not found	–	–	–	–	502	6	3	Shin et al. 2017
31	*B. kribbi*	R2F3-3-3 = KCTC 15460 = JCM 31391	human feces	Not found	–	–	–	–	8	1	1	Shin et al. 2017
32	*B. luti*	UasXn-3 = JCM 19020 = DSM 26991	methanogenic sludge	FQTV00000000.1	1	4.1	3129	36.8	346	3	2	Hatamoto et al. 2014
33	*B. massiliensis*	B84634 = CCUG 48901 = CIP 107942 = JCM 13223	a newborn blood culture	ARDF00000000.1	4	4.5	3527	42.7	694	19	11	Fenner et al. 2005
34	*B. mediterraneensis*	Marseille-P2644T = CSURP2644	ileum specimen	FQRZ00000000.1	1	4.1	3309	47.5	19	3	3	Mailhe et al. 2016
35	*B. neonati*	MS4	premature neonate stool sample	GCA_000499785.1	2	5.02	4102	43.5	1	1	1	Cassir et al. 2014
36	*B. nordii*	WAL 11050 = ATCC BAA-998 = CCUG 48943 = JCM 12987	human intestinal origin	BAJA00000000.1	3	5.6	4032	40.6	289	8	5	Song et al. 2004
37	*B. oleiciplenus*	YIT 12058 = DSM 22535 = JCM 16102	human feces	ADLF00000000.1	3	6.5	4676	43.5	105	4	3	Watanabe et al. 2010
38	*B. ovatus*	ATCC 8483 = BCRC 10623 = CCUG 4943 = CIP 103756 = DSM 1896 = JCM 5824 = NCTC 11153	human feces	CP012938.1	44	6.7	5013	41.9	7180	476	304	Eggerth and Gagnon 1933

39	*B. paurosaccharolyticus*	WK042 = DSM 21004 = JCM 15092	methanogenic reactor treating waste from cattle farms	BAJR00000000.1	2	2.8	2450	36	38	2	2	Ueki et al. 2011
40	*B. pectinophilus*	N3 = ATCC 43243	human intestinal tract	ABVQ01000036	1	3.0	2623	41.9	182	3	2	Jensen and Canale-Parola 1986
41	*B. plebeius*	M12 = DSM 17135 = JCM 12973	human feces	ABQC00000000.2	21	4.0	3195	44.3	651	33	20	Kitahara et al. 2005
42	*B. polypragmatus*	GP4 = NRC 2288	Not found	–	–	–	–	–	93	3	2	Yarza et al. 2013
43	*B. propionicifaciens*	SV434 = DSM 19291 = JCM 14649	methanogenic reactor treating waste from cattle farms	AQWS00000000.1	2	2.6	2056	38	118	3	2	Ueki et al. 2008
44	*B. pyogenes* = (*B. suis* = *B. tectus*)	P 39-88 = ATCC 35418 = CCUG 15419 = DSM 20611 = JCM 6294	abscesses and feces of pigs	ATZH00000000.1	6	3.4	2732	45.95	25000	389	230	Benno, Watabe, and Mitsuoka 1983; Sakamoto, Suzuki, and Benno 2010
45	*B. reticulotermitis*	Rs-03 = CCUG 62153 = JCM 10512	subterranean termite gut	BAIV00000000.1	1	5.4	3271	43.3	33	4	2	Sakamoto and Ohkuma 2013
46	*B. rodentium*	ST28 = CCUG 59334 = JCM 16496	chinchilla lanigera feces	BAKJ01000001.1	1	4.9	2933	47.1	2880	35	10	Kitahara et al. 2011
47	*B. salanitronis*	BL78 = DSM 18170 = JCM 13657	chicken cecum	CP002530.1	1	4.3	3626	46.44	186	9	6	Lan et al. 2006
48	*B. salyersae*	WAL 10018 = ATCC BAA-997 = CCUG 48945 = DSM 18765 = JCM 12988	human intestinal	AQHX00000000.1	7	5.6	4193	41.9	49	1	1	Song et al. 2004
49	*B. sartorii* = *B. chinchillae*	A-C2-0 = CCUG 57211 = DSM 21941 = JCM 17136	mouse cecal samples	BAKM01000001.1	4	5.4	3972	43.85	106	6	3	Clavel et al. 2010; Sakamoto and Ohkuma 2012
50	*B. stercorirosoris*	ST161 = CCUG 60872 = JCM 17103	chinchilla lanigera feces	BAKL00000000.1	3	6.2	3934	44.6	46	1	1	Kitahara et al. 2012
51	*B. stercoris*	ATCC 43183 = CCUG 38733 = CIP 104203 = JCM 9496 = NCTC 13053 = VPI B5-21	human feces	ABFZ00000000.2	33	4.0	3257	46	3130	72	39	Johnson, Moore, and Moore 1986
52	*B. thetaiotaomicron*	ATCC 29148 = CCUG 10774 = CIP 104206 = DSM 2079 = JCM 5827 = NCTC 10582 = VPI 5482	human feces	AE015928.1	39	6.4	4764	42.9	16900	1546	856	Skerman, McGowan, and Sneath 1980b
53	*B. uniformis*	ATCC 8492 = CCUG 4942 = CIP 103695 = DSM 6597 = JCM 5828 = NCTC 13054	human feces	AAYH00000000.2	69	4.7	3787	46.4	5210	315	191	Eggerth and Gagnon 1933
54	*B. vulgatus*	ATCC 8482 = CCUG 4940 = CIP 103714 = DSM 1447 = NBRC 14291 = JCM 5826 = LMG 7956 = LMG 17767 = NCTC 11154	human feces	CP000139	88	5.0	4037	42.2	11000	799	483	Eggerth and Gagnon 1933
55	*B. xylanisolvens*	XB1A = CCUG 53782 = DSM 18836 = JCM 15633	human feces	FP929033.1	21	6.1	4600	42	677	49	36	Chassard et al. 2008
56	*B. xylanolyticus*	X5-1 = CCUG 48289 = DSM 3808	methane producing cattle manure	PTJA00000000.1	1	5.6	5175	41.8	151	16	6	Scholten-Koerselman et al. 1986

Note: Data were obtained from the literature and the List of Prokaryotic names with Standing in Nomenclature (https://lpsn.dsmz.de/. . . . .).

colon carcinoma cells (Cruz-Bravo et al. 2014). Butyrate can play a key role in ameliorating intestinal barrier dysfunction (Elamin et al. 2013). These unique physiological characteristics, however, could also cause adverse effects on the host. For example, although the capsular polysaccharide A (PSA) of *B. fragilis* is widely considered to play a role in alleviating *Helicobacter hepaticus* (*H. hepaticus*)-induced colitis (Mazmanian, Round, and Kasper 2008), it has also been found to possess abscess-inducing properties (Surana and Kasper 2012). The polysaccharide-metabolizing abilities of *Bacteroides thetaiotaomicron* (*B. thetaiotaomicron*) have also been reported to facilitate the growth of pathogenic bacteria *Clostridium difficile* (*C. difficile*), to enhance virulence gene expression in enterohemorrhagic *Escherichia coli* (*E. coli*), and to exacerbate *Citrobacter rodentium* (*C. rodentium*) infection (Curtis et al. 2014). Additionally, a recent report also described the role of enterotoxigenic *B. fragilis* (ETBF) in human disease (Sears 2009). These results suggest that *Bacteroides* employed various survival strategy as inhabitant of human intestinal tract, some of which may be beneficial while others may cause aberration to the host.

Most studies about *Bacteroides* have been focused on nine species including *B. fragilis, B. thetaiotaomicron, Bacteroides ovatus* (*B. ovatus*), *Bacteroides uniformis* (*B. uniformis*), *Bacteroides vulgatus* (*B. vulgatus*), *Bacteroides xylanisolvens* (*B. xylanisolvens*), *Bacteroides acidifaciens* (*B. acidifaciens*), *Bacteroides dorei* (*B. dorei*) and *Bacteroides caccae* (*B. caccae*). This review provides a comprehensive understanding of the physiological and functional roles of these nine *Bacteroides* species in human health and diseases. Besides, we also discussed the current methods used in the safety evaluation of *Bacteroides* species as well as key opinions about the concerns of these strains for the future use.

B. fragilis

B. fragilis is a common resident of the human gastrointestinal tract (Patrick et al. 2011). The abundance of *B. fragilis* accounts for only up to 1% of the total gut microbial population (Rocha and Smith 2013) and approximately 2% of the total *Bacteroides* population in the human intestinal tract (Tajkarimi and Wexler 2017), while this low-abundant species plays an important role in alleviating disease conditions (Mazmanian, Round, and Kasper 2008; Ochoa-Repáraz et al. 2010; Hsiao et al. 2013) and restoring systemic immune defects (Mazmanian et al. 2005). Thus, it has been widely recommended as a potential probiotic (Troy and Kasper 2010; Hsiao et al. 2013; Deng et al. 2016) (Table 2). However, its adverse effects on human health should not be ignored (Table 3). *B. fragilis* toxin, a kind of zinc-dependent metalloprotease with broad proteolytic specificity, was encoded by fragilysin (*bft*) gene (Pierce and Bernstein 2016) with three isoforms (*bft*-1, *bft*-2, and *bft*-3). It hydrolyzes actin, fibrinogen and etc., finally disrupt the intestinal epithelial barrier and cause morphological and functional alterations (Nakano and Avila-Campos 2004) (Figure 2). Besides, Hwang et al. reported that azoxymethane (AOM)/dextran sulfate sodium (DSS)-treated BALB/c mice orally inoculated

Table 2. Mechanisms of *Bacteroides* species in host health.

Probiotic strains	Disease	Effects	Model	Reference
B. fragilis JCM10556	Diabetes and obesity	insulin levels in serum↑, serum glucagon-like peptide-1↑, intestinal dipeptidyl peptidase-4 ↓	$Atg7^{\Delta CD11c}$ mice, $Atg7^{f/f}$ mice and C57BL/6 mice	Yang et al. 2017
B. fragilis NCTC 9343	Colitis induced by *H. hepaticus*	TNF-α↓, IL-17↓, IL-10↑	$Rag^{-/-}$ mice, $Il10^{-/-}$ donor mice, wild-type (C57BL/6) mice.	Mazmanian, Round, and Kasper 2008
B. fragilis NCTC 9343	CNS demyelination	Foxp3+ Treg cells↑, IL-10↑	IL-10-deficient mice	Ochoa-Repáraz et al. 2010
B. fragilis NCTC 9343	*B. henselae*-induced damage	*B. fragilis* colonization could decrease the number of positive cells per field in the liver, aorta and spleen sections and restore the EPC decrease observed in mice infected with *B. hensela*.	C57BL/6J mice	Sommese et al. 2012
B. fragilis NCTC 9343	Autism spectrum disorder	Oral treatment with *B. fragilis* NCTC 9343 could help correct gut permeability, alter microbial composition, and ameliorate defects in communicative, stereotypic, anxiety-like and sensorimotor behaviors.	C57BL/6N mice	Hsiao et al. 2013
B. fragilis ZY-312	AAD	Oral treatment with *B. fragilis* ZY-312 could ameliorate the gastroin-testinal symptoms of AAD in rats by modulating gut microbiota, thereby restoring epithelial cell organization and barrier function	Sprague-Dawley rats	Zhang et al. 2018
B. thetaiotaomicron VPI-5482	Capillary network formation	The capillary network formation can be restarted and completed within 10 days after colonization with *B. thetaiotaomicron* VPI-5482.	germ-free mice	Stappenbeck, Hooper, and Gordon 2002
B. thetaiotaomicron VPI-5482	Obesity	serum glutamate concentration↓, the fat decomposition↑ and fatty acid oxidation process of fat cells↑, fat accumulation↓, delaying the rate of weight gain and the degree of obesity↓	C57BL6 mice	Liu et al. 2017
B. ovatus	DSS-induced chronic colitis	minor morphological changes in colon tissue, jejunal brushborder enzyme activities such as γ-glutamyltranspeptidase, lactase and alkaline phosphatase↓	BALB/c and SCID mice, Germ-free and *B. ovatus*-associated mice	Hudcovic et al. 2009
B. uniformis CECT 7771	Obesity	body weight gain↓, liver steatosis↓, liver cholesterol↓, triglyceride concentrations ↓, small adipocyte numbers↑, serum cholesterol, triglyceride, glucose, insulin and leptin levels↓, dietary fat absorption↓, improved immune defence mechanisms, impaired in obesity, TNF-α production and phagocytosis↑	C57BL6 mice	Gauffin Cano et al. 2012
B. vulgatus mpk	*Y. enterocolitica*-induced colitis	*B. vulgatus* mpk could inhibit the *Y. enterocolitica*-induced NF-κB activation and IL-8 production in EC.	C57BL6 mice	Frick et al. 2007

CNS, Central nervous system; *H. hepaticus, Helicobacter hepaticus; B. henselae, Bartonella henselae;* AAD, Antibiotic-associated diarrhea; DSS, Dextran-sodium sulfate; *Y. enterocolitica, Yersinia enterocolitica;* EPC, Endothelial progenitor cell; EC, Epithelial cells.

Table 3. Mechanisms of *Bacteroides* species in host diseases.

Pathogenic strains	Disease	Effects	Model	Reference
B. fragilis VPI 13784	Colitis	Colonic histopathology demonstrated mucosal thickening with inflammatory cell infiltration, crypt abscesses, and epithelial cell exfoliation, erosion, and ulceration.	C57BL/6J or germ-free 129S6/SvEv mice	Rhee et al. 2009
B. fragilis NCTC 9343	Colitis	ETBF rapidly activates mucosal immune cell Stat3. Subsequently, increased mucosal permeability occurs, together with increased mucosal immune cell Stat3 activation and Stat3 activation in colonic epithelial cells.	C57BL/6 wild-type, C57BL/6$^{Stat3\Delta IEC}$ and Rag-1 mice	Wick et al. 2014
B. fragilis 86-5443-2-2	Murine colon tumorigenesis	Combined action of the *B. fragilis* enterotoxin BFT and IL-17 on colonic epithelial cells promoted the differentiation of MO-MDSCs, which selectively upregulated Arg1 and Nos2, produced NO, and suppressed T-cell proliferatio.	C57BL/6 (WT), CD45.1 C57BL/6 and MinApc716/p (Min) mice	Thiele Orberg et al. 2017
B. fragilis 86-5443-2-2	IBD	Oral treatment with *B. fragilis* 86-5443-2-2 could experience worse colitis reflected by less weight gain, enhanced gross disease, and greater inflammation in their colons, especially in the cecum.	Male C57BL/6 mice	Rabizadeh et al. 2007
B. vulgatus (isolated from a guinea pig with carrageenan-induced colitis)	Colitis	*B. vulgatus* for 32 weeks developed only mild colonic inflammation in IL-10-deficient mice.	Wild-type C57BL/6 mice, heterozygous C57BL/6 mice and IL-10-deficient mice	Sellon et al. 1998

ETBF, enterotoxigenic *Bacteroides fragilis*; BFT, *B. fragilis* enterotoxin; IBD, inflammatory bowel disease; MO-MDSCs, monocytic myeloid-derived suppressor cells; Arg1, arginase 1; NO, nitric oxide.

with *B. fragilis* overexpressing *bft* developed numerous polyps whereas mice infected with *B. fragilis* carrying a biologically inactive *bft* did not promote polyp formation (Hwang et al. 2020). These results protrude the pathogenicity of *bft*. Therefore, according to *bft* occurrence in the genome, *B. fragilis* has been classified into two subtypes: non-enterotoxigenic (NTBF, lack of *bft*) and enterotoxigenic (ETBF, with *bft*) *B. fragilis*.

B. fragilis NCTC9343 is a NTBF type strain and one of the most studied *B. fragilis* strains with potential probiotic functions. Oral administration of this strain has been demonstrated to protect against intestinal inflammatory disease (Mazmanian, Round, and Kasper 2008), central nervous system (CNS) demyelinating disease (Ochoa-Repáraz et al. 2010), *Bartonella henselae* (*B. henselae*)-induced damage (Sommese et al. 2012) in mouse models. And it also plays a role in alleviating autism spectrum disorder (Hsiao et al. 2013). The underlying mechanism might be associated with the Polysaccharide A (PSA) of *B. fragilis* NCTC9343. Recent studies showed that purified PSA of *B. fragilis* NCTC9343 can induce the secretion of anti-inflammatory interleukin (IL)-10 (Rubtsov et al. 2008), which could help protect against inflammatory disease (Mazmanian, Round, and Kasper 2008) and viral encephalitis (Ramakrishna et al. 2019) (Figure 1). Importantly, PSA binding by B cells is essential for induction of regulatory $CD4^+$ and $CD8^+$ T cells secreting IL-10 to control innate inflammatory responses (Ramakrishna et al. 2019). Interestingly, in the absence of antigen-presenting cells (APC), PSA could directly prompt Toll-like receptors 2 (TLR2) expressed by Foxp3+ Tregs to induce immune regulatory functions (Round et al. 2011) (Figure 1). Besides, *B. fragilis* has also been reported to inhibit the colonization of pathogenic bacteria both in vitro and in vivo. A study by Li et al. indicated that *B. fragilis* could inhibit the growth of *Vibrio parahaemolyticus* and protect *V. parahaemolyticus*-induced damages in both RAW 264.7 and LoVo cells. (Li et al. 2017). An in vivo test by Hecht et al. showed that the competitive exclusion of ETBF by a NTBF strain limited toxin exposure and protected the host against intestinal inflammatory disease dependent upon type VI secretion (Hecht et al. 2016). However, it is difficult to prove the causal relationship in these mice models because improvements in disease indexes are always accompanied by improvements in the balance of gut microbial composition. It is important for future understanding on how the gut microbiota establish within hosts, influence health and diseases, and offer insights into potential future applications (García-Bayona and Comstock 2018). Several studies provided evidence that *B. fragilis* plays an important role in the regulation of intestinal microbiota. For example, *B. fragilis* ZY-312 has been reported to prevent antibiotic-associated diarrhea in rats (Zhang et al. 2018). This strain could also significantly modulate the compositions of the intestinal bacterial communities in rats, and suppress *Cronobacter sakazakii*-induced necrotizing enterocolitis by modulating the proinflammatory response and dual cell death (Fan et al. 2019).

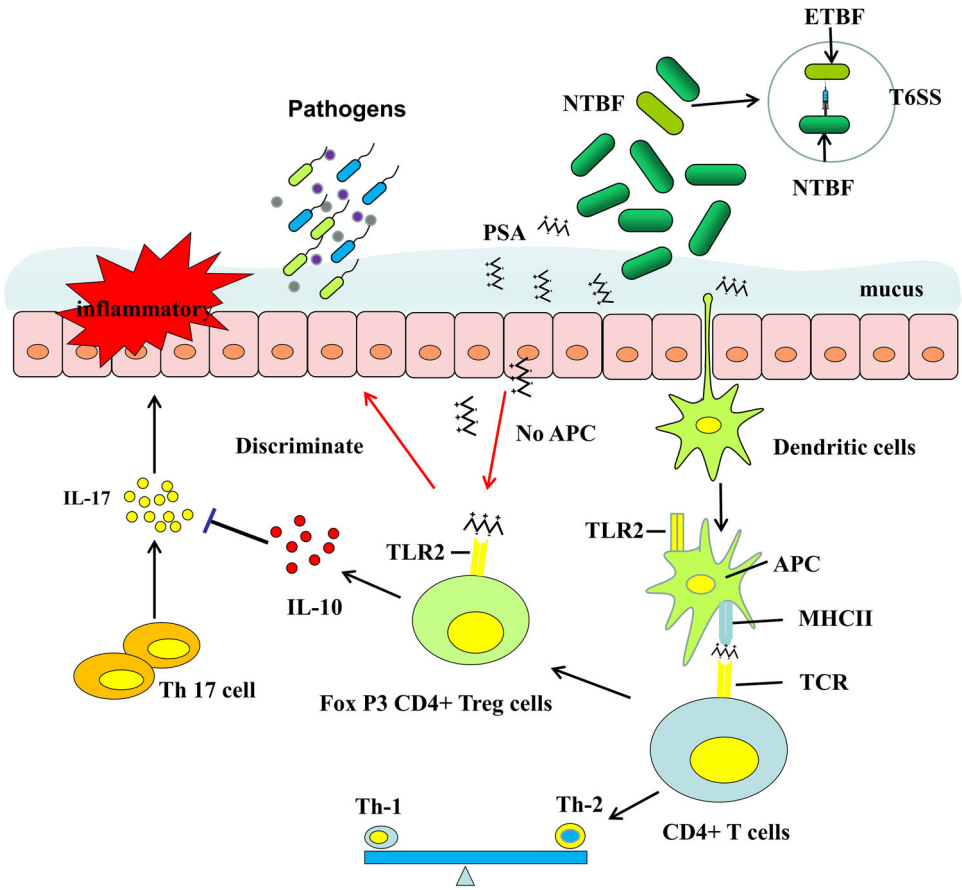

Figure 1. Non-enterotoxigenic *B. fragilis* regulates gut immune homeostasis. (i) PSA can induce cellular and physical development of the immune system and corrects the imbalance of Th1/Th2 cells in GF mice. PSA is recognized by plasmacytoid dendritic cells in a TLR2-dependent manner and presented by MHCII molecules and costimulatory molecules to induce Treg cells. Moreover, the PSA enveloped in outer membrane vesicles of *B. fragilis* was delivered to intestinal dendritic cells, which induced IL-10 production by CD4+ Foxp3+ regulatory T cells (Tregs) (Allan et al. 2008; Mazmanian, Round, and Kasper 2008; Round and Mazmanian 2010). (ii) in the absence of APC, PSA could directly prompt TLR2 expressed by Foxp3+ Tregs to induce immune regulatory functions (Round et al. 2011). TLRs are essential components of the body's innate immune system that can recognize the endotoxins.Note: APC, antigen-presenting cells; MHCII, major histocompatibility class II; TLR2, Toll-like receptors 2.

The first ETBF strain was isolated from newborn lambs with diarrheal disease, and this was the first study to describe the association of *B. fragilis* with diarrheal disease (Myers et al. 1987). Thereafter, using in vitro testing, some studies reported the adverse effects of ETBF, mainly the potentials to induce inflammatory bowel disease (IBD) (Prindiville et al. 2000; Basset et al. 2004; Rhee et al. 2009; Wick et al. 2014) and colorectal cancer (Thiele Orberg et al. 2017). It has been demonstrated that *bft* can bind to the intestinal epithelial cell receptor and stimulate signal transduction pathways, and thereby increase the epithelial barrier permeability, change colonic epithelial cell (CEC) morphology (Obiso, Azghani, and Wilkins 1997) and induce CEC proliferation (Wu et al. 2003) (Figure 2). These effects were confirmed by several in vivo experiments. Rabizadeh et al. (2007) found that ETBF plays a role in the development and progression of colitis in mice treated with DSS. Another study demonstrated that ETBF could induce acute symptomatic colitis and persistent subclinical colonic inflammation and hyperplasia in a murine model (Rhee et al. 2009) because of E-cadherin cleavage that induced CEC hyperplasia and secretion of the chemokine KC (the murine IL-8 analog). These in vivo experiments support the results of in vitro experiments. Taken together, these results indicate that *bft* is the main factor involved in the induction of colitis or cancer in both conventional wild-type and germ-free mice. In addition, physiological and genome analyses have indicated that the pathogenic factors of *B. fragilis* may be derived from its complex bacterial components and metabolites, such as lipopolysaccharide (LPS) (Mancuso et al. 2005), enterotoxin, endotoxin (Meiselmikolajczyk et al. 2003), ferritin (Rocha and Smith 2004), and metalloprotease (Kato et al. 2000), all of which can also be considered as the main indicators for the safety evaluation of *B. fragilis*.

Current studies on *B. fragilis* strains (such as *B. fragilis* NCTC9343 and *B. fragilis* ZY-312) showed the protective effects of strains on inflammatory disease (Mazmanian, Round, and Kasper 2008), *B. henselae*-induced gut damage (Sommese et al. 2012) and antibiotic-associated diarrhea (Zhang et al. 2018). These results provide an idea that certain *B. fragilis* strains could be applied for adjuvant therapy against intestinal inflammations. However, the safety and efficiency of these strains need to be further validated to fully understand the potential side effects of these strains.

B. thetaiotaomicron

B. thetaiotaomicron, originally isolated from the feces of healthy adult humans (Xu et al. 2003), is one of the more

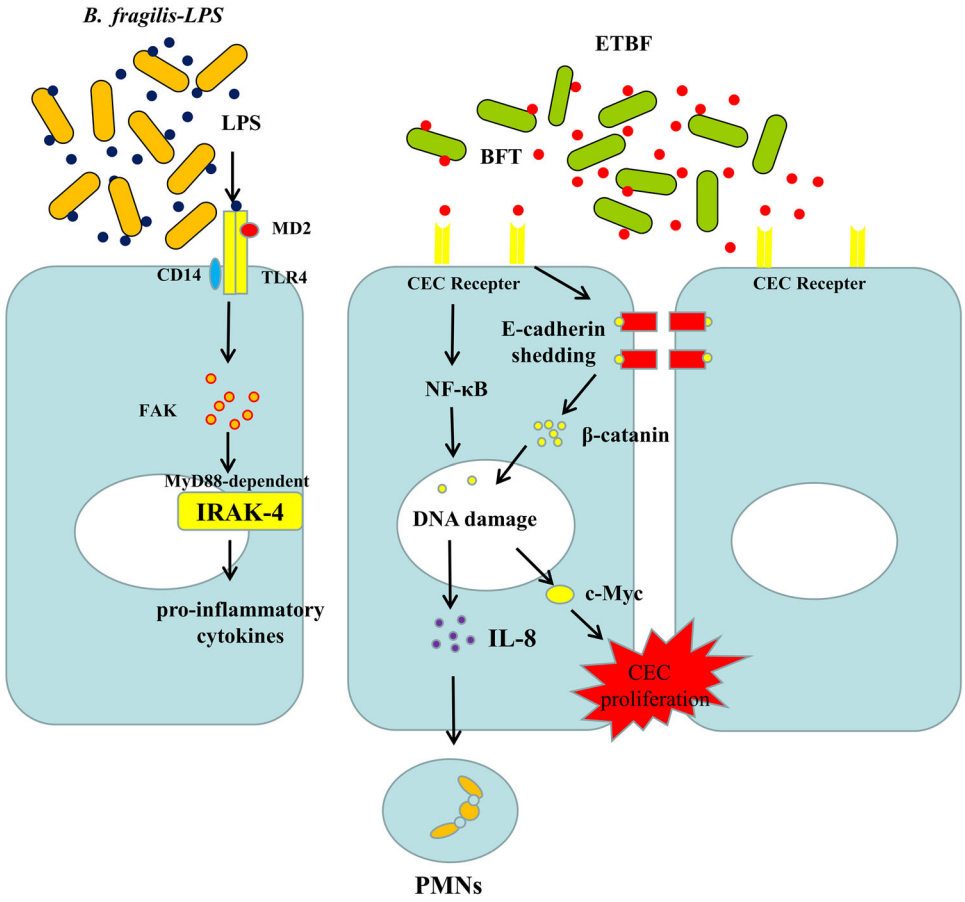

Figure 2. Potential pathogenicity of *B. fragilis*. ETBF can secrete BFT, which can binds to a specific, but uncharacterized CEC receptor, triggering a marked array of CEC signal transduction, E-cadherin cleavage, Wnt signaling, and secretion of proinflammatory cytokines contributing to crucial aspects of: (i) an increase in the epithelial barrier permeability and changes in CEC morphology (Obiso, Azghani, and Wilkins 1997) associated with E-cadherin shedding; (ii) induction of c-Myc expression that can further induces CEC proliferation (Wu et al. 2003); (iii) activation of NF-κB (Kim et al. 2002) to induce IL-8 expression by human CECs (Sanfilippo et al. 2010; Wu et al. 2004). LPS from *B. fragilis*, at physiologically relevant concentrations, causes an activation of the TLR-4 signal transduction cascade, which leads to the phosphorylation and activation of the intestinal epithelial cell FAK. The activated enterocyte FAK regulates the activation of MyD88 and IRAK4 to promote the expression of pro-inflammatory cytokines and damage the tight junction of epithelial walls (Guo et al. 2013; Guo et al. 2015).Note: LPS: Lipopolysaccharides; NF-κB, nuclear factor-kappa B; CEC, colonic epithelial cell; TLR4, Toll-like receptor-4; FAK, focal adhesion kinase.

adaptable intestinal bacteria (Hochart-Behra et al. 2014). It is a common member of our normal distal intestinal microbiota (Moore and Holdeman 1974), accounting for up to 6% of all bacteria and 12% of the total *Bacteroides* population in the human intestine (Zocco et al. 2007). Nowadays, it has been considered as a genetically manipulable model organism to understand the role of *Bacteroides* in human health and diseases (Zocco et al. 2007).

Some studies have shown that *B. thetaiotaomicron* can degrade a wide range of dietary polysaccharides in vitro (Xu and Gordon 2003) and has the competitive ability to thrive in various niches in the host (Porter et al. 2017). This ability is reflected in its genome (Xu et al. 2003). *B. thetaiotaomicron* ATCC 29148 (VPI 5482), the type and widely studied *B. thetaiotaomicron* strain, has the largest ensemble of genes involved in acquiring and metabolizing carbohydrates, which includes 163 paralogs of two outer membrane proteins (SusC and SusD) that bind and import starch (Shipman, Berleman, and Salyers 2000) and 172 glycosyl hydrolases (Xu et al. 2003), 11% of which are present on the outer membrane or are released extracellularly (Xu et al. 2003). Interestingly, the CAZy database shows the human genome (2.85 Gb) encodes only 98 enzymes that are known or predicted to hydrolyze glycosides and does not encode any enzyme required for degrading common components of plant fibers, such as xylan, pectin, and arabinose. This is a strong evidence that the *B. thetaiotaomicron* can help host digest and utilize non-digestible polysaccharides.

Based on these findings, some studies have speculated that *B. thetaiotaomicron* could be associated with obesity because of its ability to use polysaccharide and regulate fat metabolism (Bäckhed et al. 2004). One study showed that the *B. thetaiotaomicron* type strain VPI-5482 from normal mice could increase the body fat content of germ-free mice because of the inhibition of fasting-induced adipocyte factor (Fiaf) that can inhibit lipoprotein lipase activity, reduce fat accumulation, and promote fat utilization (Bäckhed et al. 2004). In contrast, metabolomics analysis and in vivo experiments in mice in other studies have demonstrated that *B. thetaiotaomicron* VPI-5482 could reduce the serum glutamate concentration, increase fat decomposition, and accelerate fatty acid oxidation in fat cells, thereby reducing fat accumulation, delaying the rate of weight gain and reducing the degree of obesity (Liu et al. 2017) (Table 2). Besides, one study showed that the supplementation of *B. thetaiotaomicron* could significantly change the abundance of

Akkermansia muciniphila, whereas *A. muciniphila* could relieve gut inflammation in high-fat diet-fed (HFD) mice (Everard et al. 2013). This phenomenon can be explained by the role of these two species in maintaining the epithelial barrier (Hooper et al. 2001; Everard et al. 2013).

In particular, the depletion of the population of these species may increase LPS transport to circulation, thereby inducing the expression of pro-inflammatory factors, such as tumor necrosis factor alpha and IL-6 (Qian and Cao 2013). Notably, this variation could contribute to the anti-obesity effect of *B. thetaiotaomicron* under a specific intestinal microenvironment. *B. thetaiotaomicron* has also been reported as a symbiont that imparts anti-inflammatory effects via two main mechanisms: the anti-inflammatory effect on Caco-2 cells via the peroxisome proliferator-activated receptor gamma pathway (Kelly et al. 2004) and consistent induction of high IL-8 levels in both ileal and colonic tissues in Crohn's disease (Edwards et al. 2011). This finding has provided new cellular targets for therapeutic drug design and interventions for treating chronic inflammation. Interestingly, some studies have stated that the probiotic effects of *B. thetaiotaomicron* include not only the reduction of obesity or inflammation but also an increase in the capillary network formation in germ-free mice via Paneth cells (Stappenbeck, Hooper, and Gordon 2002) (Table 2) and inhibition of rotavirus infection by modulation of the apical glycosylation pattern of cultured human intestinal HT29-MTX cells (Freitas et al. 2003).

Nevertheless, as an anaerobic opportunistic pathogen, *B. thetaiotaomicron* was considered as a common infectious anaerobic gram-negative bacterium, although it had rarely been isolated (Miragliotta et al. 2006). Recent studies have reported that it can be isolated from some human lesions, including patients with cholesteatoma and meningitis (Feuillet et al. 2005), abdominal aortic aneurysm (Maeda et al. 2011), disseminated multiple myeloma (Agarwal, Hansberry, and Goldstein 2014), and mycotic abdominal aortic aneurysm (Kim et al. 2014), suggesting that this microbe has some potential negative effects. Further studies have reported that bacteremia due to *B. thetaiotaomicron* is associated with 100% mortality rates (Chow and Guze 1974; Brook 1990) and that *B. thetaiotaomicron* can potentially cause some diseases in humans, such as endogenous suppurative and septic *B. fragilis* group-induced infections (Werner 1974; Höffler 1987). These results suggested that *B. thetaiotaomicron* is more virulent than other anaerobes. However, none of these reports have suggested a direct evidence of the involvement of *B. thetaiotaomicron* in disease pathogenesis. Notably, a well-characterized human isolate of *B. thetaiotaomicron* has been reported to induce mild colitis in HLA-B27 transgenic rats, thus implicating *B. thetaiotaomicron* in IBD pathogenesis (Hansen et al. 2012). This finding may reveal novel pathways involved in the development and progression of IBD. In addition, although *B. thetaiotaomicron* expresses sialidase enzymes, it cannot metabolize sialic acid. This could also contribute to the growth of pathogenic bacteria that use sialic acid as a carbon source, such as *C. difficile* (Bäumler and Sperandio 2016); and finally enhances virulence gene expression of enterohemorrhagic *E. coli*; and exacerbates *C. rodentium* infection (Curtis et al. 2014), implying that certain enteric pathogens can exploit other microbes to enhance their virulence. Therefore, unraveling the interactions between *B. thetaiotaomicron* and pathogenic bacteria in the gut will elucidate new treatment strategies for infectious diseases.

Based on current studies, including genomic analysis, cell experiments and animal experiments, certain *B. thetaiotaomicron* strains showed the ability to regulate lipid metabolism and to alleviate obesity (Bäckhed et al. 2004). However, there is no valid evidence to verify *B. thetaiotaomicron* can be used to reduce obesity in humans. In addition, there is a lack of robust safety evaluation for the use of *B. thetaiotaomicron* in humans. Thus, strict screening and safety assessment standards should be established for the further application of these bacterial species.

B. ovatus

B. ovatus, first isolated from human feces in 1933 (Eggerth and Gagnon 1933), can use xylan as the sole source of carbohydrate (Weaver et al. 1992), and be able to grow on all known plant hemicelluloses (Salyers et al. 1977) and some complex plant cell wall polysaccharides, such as β-mannan-based dietary fibers (Valentine and Salyers 1992). Recently, it has also been considered as one of the representatives of the *Bacteroides* genus because of its immune regulatory ability (Tan et al. 2019).

Some recent studies have reported that *B. ovatus* is a symbiont with anti-inflammatory properties such as relieving LPS-induced inflammation, promoting intestinal homeostasis (Tan et al. 2019) and protecting DSS-induced chronic colitis in mice (Hudcovic et al. 2009), all of which imply the potential probiotic roles of wild-type *B. ovatus* in human health (Table 2). Interestingly, some studies have also shown that similar effects can be achieved using engineered strains. An engineered *Bacteroides* strain (BO-KGF) can produce biologically active keratinocyte growth factor or secrete human transforming growth factor beta 1 in the presence of dietary xylan 1, which prevents DSS-induced chronic colitis and limits the disruption of the epithelial barrier (Hamady et al. 2010; Hamady et al. 2011). Meanwhile, engineered *B. ovatus* V975 can produce active murine IL-2 in response to xylan (Farrar et al. 2005). These findings suggest new potential long-term immunotherapies for chronic gut disorders. In addition, *B. ovatus* D-6 can express an immune-accessible α-anomeric Thomsen-Friedenreich antigen (TFα) on its surface (Henderson et al. 2011). This feature has been further confirmed in one study, which demonstrated that *B. ovatus* D-6 could expressed an effective target, namely the tumor-specific TFα, for a cancer vaccine that can activate specific anti-TFα antibodies in vivo (Ulsemer et al. 2013). This finding provided a new research focus on which it may alleviate cancer.

One report described that *B. ovatus* causes a systemic antibody response in IBD (Saitoh et al. 2002), suggesting that it is so highly antigenic that it evades the anti-inflammatory regulation exerted by an immunoglobulin (Ig) A response and can thus cause an IgG response. However, no direct

evidence is available to indicate whether these molecules play a direct pathogenic role in the gut tissue (Saitoh et al. 2002).

B. uniformis

B. uniformis, originally isolated from human feces (Eggerth and Gagnon 1933), is present in high abundance in the human gastrointestinal tract (Zitomersky, Coyne, and Comstock 2011), and its abundance is often low in anaerobic infections (Hedberg et al. 1995). Recently, some reports have confirmed that it exhibits a significant glycolytic capability (Tasse et al. 2010) and its dietary fiber-degrading ability is not limited to the colon but also extends to the distal regions of the small intestine such as ileum (Patrascu et al. 2017). *B. uniformis* CECT 7771 was the most studied strain and was previously considered a potential probiotic (Fernández-Murga and Sanz 2016). It possesses significant glycolytic capability. Furthermore, it could modulate its metabolic pathways to adapt to different gut environments, such as responses to dietary fibers (Benítez-Páez, Gómez del Pulgar, and Sanz 2017), which finally explains its diverse effects on host health.

Studies have shown that the low abundance of *B. uniformis* in the intestines of formula-fed infants is associated with a high risk of obesity (Owen et al. 2005; Sánchez et al. 2011), suggesting that *B. uniformis* plays a potential role in alleviating obesity. This speculation was supported by the results of another study which demonstrated that the effects of *B. uniformis* CECT 7771 on obesity-related metabolic and immune alterations were promoted by feeding mice with diet supplemented with *B. uniformis* CECT (Gauffin Cano et al. 2012) (Table 2). Oral administration of *B. uniformis* CECT 7771 can alleviate the metabolic and immune dysfunctions associated with obesity in mice, such as body weight gain and liver steatosis; reduce liver cholesterol and triglyceride concentrations (Gauffin Cano et al. 2012). In addition, it could partially restore the HFD microbiota-induced alterations, suggesting the involvement of both direct and indirect microbiota-mediated mechanisms (Neef and Sanz 2013). However, the precise molecular mechanisms remain to be elucidated to explain the metabolic and immune effects observed in this obesity model (Neef and Sanz 2013). Another potential probiotic function of *B. uniformis* is the reduction of acyl carrier protein expression, a fundamental component required for LPS biosynthesis in gram-negative bacteria and their growth and survival (Galloway and Raetz 1990; Belunis et al. 1995; Masoudi et al. 2014). LPS can promote the expression of pro-inflammatory cytokines and lead to chronic low-grade inflammation observed in obesity (Cani et al. 2007). Thus, *B. uniformis* could have a beneficial effect in alleviating inflammation.

In 2015, one case report described the isolation of *Aggregatibacter aphrophilus* and *B. uniformis* from brain abscess and confirmed that this combination of microorganisms was the cause of the abscess (Bogdan et al. 2015). However, no other study has reported a more direct or supporting evidence regarding this harmful effect.

B. vulgatus

B. vulgatus was originally obtained from human feces (Eggerth and Gagnon 1933). It has also been isolated from clinical specimens of patients (Holland, Hill, and Altemeier 1977), especially those with IBD (Conte et al. 2006; Lucke et al. 2006). One study showed that *B. vulgatus* accounts for more than 40% of the total gut microbiota of patients with Crohn's disease, but only 6% of the total gut microbiota of healthy humans (Wensinck et al. 1981; Ruseler-van Embden and Both-Patoir 1983). Therefore, it was also widely considered as a representative of the *Bacteroides* genus associated with IBD. It could be linked to its ability to attach and invade CECs and induce the expression of proinflammatory cytokines (Ohkusa et al. 2009), implicating its pathogenicity in IBD development. This hypothesis has been proven in both animal and clinical experiments. Studies have found that six common intestinal inhabitants, including *B. vulgatus*, isolated from colitis patients or guinea pigs, could cause colitis and gastritis in HLA-B27 transgenic rats (Rath et al. 1996) and that *B. vulgatus* alone could be more potent than *E. coli* alone in inducing colitis (Rath, Wilson, and Sartor 1999). Similar results were reported by other studies on humans (Bamba et al. 1995; Matsuda et al. 2000), supporting that *B. vulgatus* is capable of invading CECs (Ohkusa et al. 2009), inducing the expression of pro-inflammatory cytokines (Rath, Wilson, and Sartor 1999; Ohkusa et al. 2009; Kishi et al. 2000), and adhering to the colonic tissue in patients with ulcerative colitis (Sato et al. 2010).

A few studies have described the role of *B. vulgatus* in relieving inflammation in mice. One study reported that *B. vulgatus* mpk has potential probiotic properties with an ability to protect against *E. coli* mpk-induced colitis development in IL-$2^{-/-}$ mice (Waidmann et al. 2003) (Table 2), but underlying mechanism has not been elucidated. Another study reported the ambiguous role of IL-6 secreted by *B. vulgatus* mpk in inflammatory diseases (Frick et al. 2006) (Figure 4). This study showed that IL-6 could prevent colitis by inducing semi-mature dendrite cells along with the accumulation of IL-6-secreting dendrite cells in the intestine, reducing their migration to mesenteric lymph nodes, and reducing T cell activation. In contrast, *B. vulgatus* mpk could inhibit the *Yersinia enterocolitica* (*Y. enterocolitica*)-induced NF-κB activation and IL-8 production in epithelial cells (EC) (Frick et al. 2007). This finding indicates that the pathogenicity of *B. vulgatus* depends on the intestinal environment or animal models (Bloom et al. 2011; Rath, Wilson, and Sartor 1999).

Interestingly, one study reported that *B. vulgatus* ATCC 8482 is highly resistant to inorganic arsenic because of its ability to express the arsenic resistance genes (Li, Mandal, and Rosen 2016), suggesting that the probiotic effects of *B. vulgatus* also extend to the inhibition of heavy metal toxicity.

B. xylanisolvens

B. xylanisolvens, first isolated from human feces as a novel *Bacteroides* species (Chassard et al. 2008), possesses a high xylanase activity with the type strain named as XB1A (Mirande

et al. 2010). Deficiency of *B. xylanisolvens* (Chassard et al. 2008) favors the growth of other *Bacteroides* species. The genome of *B. xylanisolvens* XB1A encodeed 256 CAZymes, including glycoside hydrolases (GHs) and carbohydrate esterases (CEs), namely GH10, GH51, GH67, GH115, CE1, and CE6, that potentially hydrolyze xylans (Despres et al. 2016), and most of these genes were found to be clustered in PULs. *B. xylanisolvens* XB1A genome was predicted to contain 74 PULs (Terrapon et al. 2015). Therefore, further functional genome studies on *B. xylanisolvens* are needed to better understand its role in dietary fiber degradation and its impact on intestinal health.

A few studies have reported that *B. xylanisolvens* DSM 23964 increases the concentration of TFα-specific IgM serum antibodies, which are involved in controlling cancer development (Ulsemer et al. 2016) and exhibit no virulence in humans (Ulsemer et al. 2012c). Thus, *B. xylanisolvens* DSM 23964 has now been approved for supplementation of pasteurized milk products under Novel Food Regulation No. 258/97 by the European Commission (Brodmann et al. 2017), suggesting the great potentials of *B. xylanisolvens* as a probiotic and a foundation for further investigation of more probiotic candidates in this species.

B. acidifaciens

B. acidifaciens can grow well in bile acid and perform aesculin hydrolysis (Miyamoto and Itoh 2000) and was first isolated from mice cecum. The A40T (JCM 10556 T) is considered the type strain (Miyamoto and Itoh 2000) and can be isolated from human feces (Ott et al. 2004). Isoflavones have been demonstrated to reduce the risk of some forms of cancer and atherosclerosis (Zhuo, Melby, and Watanabe 2004; Messina, Mccaskill-Stevens, and Lampe 2006). Whereas *B. acidifaciens* is associated with human gut isoflavone degradation (Renouf and Hendrich 2011), suggesting that it plays a potential role in the development of some diseases. Meanwhile, *B. acidifaciens* JCM10556 has been shown to significantly promote IgA production in the large intestine, thereby facilitating the maintenance of intestinal mucosa by eliminating pathogens that have breached the epithelial walls (Yanagibashi et al. 2013). Reports on the probiotic effects of *B. acidifaciens*, such as prevention of obesity in mice, are limited (Yang et al. 2017) (Figure 3). Notably, *B. acidifaciens* has been shown to increase the serum glucagon-like peptide-1 level and decrease the intestinal dipeptidyl peptidase-4 level when fed to C57BL/6 mice (Yang et al. 2017). In contrast, another study found that *B. acidifaciens* may be associated with liver disease (Xie et al. 2016). Thus, it is likely that under different dietary conditions, *B. acidifaciens* may have different effects on hepatic pathophysiology.

Other bacteroides species

In addition to these *Bacteroides* species that have attracted considerable attention of researchers, some other *Bacteroides* species have shown significant interactions with the host. For example, *B. dorei* D8 has been found to prevent high-fat diet-induced cardiovascular disease in vitro because of its ability to efficiently convert cholesterol into coprostanol (Gérard et al. 2007). In addition, *B. caccae* was recognized as a biomarker of IBD as the Omp W protein produced by *B. caccae* is a target of the IBD-associated immune response (Wei et al. 2001). Accordingly, the high intestinal *B. caccae* abundance in gout patients could potentially induce serious inflammatory response.

The mechanisms of different bacteroides species in health and diseases

Bacteroides can promote host health through several ways (i) stimulating immune system; (ii) enhancing phagocytosis of macrophages; (iii) resisting the colonization of pathogenic bacteria; (iv) regulating body metabolism; (v) modulating the imbalance between pro-oxidant and anti-oxidant mechanisms; (vi) inducing the proliferation of probiotic bacteria, et al. However, the pathways and molecule mechanisms varied between *Bacteroides* species and traditional probiotics. PSA biosynthesized by *B. fragilis* specifically induced Tregs differentiation and enhanced its functions in the intestine, and thus promote secretion of more IL-10 to reduce local inflammation. However, it's noteworthy that the health promoting effects of *Bacteroides* species depend on the strain specificity and host physiological status. It has been showed that individuals with a compromised immune system have little tolerance to oral probiotics and a high risk of sepsis. Besides, some species secrete toxin and others can enhance virulence gene expression of pathogenic bacteria. The safety evaluation for *Bacteroides* species should be more serious. *B. fragilis* and *B. thetaiotaomicron* were two most studied species of *Bacteroides*. Such as *B. fragilis* can enhance the suppressive abilities of Treg cells throughout the body (Shen et al. 2012), and even induces IL-10 secreting to control innate inflammatory responses (Ramakrishna et al. 2019). *B. thetaiotaomicron* has been reported to educate the immune system. The monocolonization of *B. thetaiotaomicron* in germ-free mice promoting the fucosylation of small epithelial cells, which helps the mice to resist to the invasion of pathogenic bacteria. As the importance of precision medicine and nutrition, the exact mechanisms of specific *Bacteroides* species should be clarified to support their future development.

The safety assessment of bacteroides species

The definition of NGP has been proposed as a biological product that: (i) contains live organisms, such as bacteria; (ii) is applicable to the prevention, treatment, or cure of a disease or condition of human beings; and (iii) is not a vaccine (O'Toole, Marchesi, and Hill 2017). The genus of *Bacteroides* is a candidate of NGP. To date, there is only one *Bacteroides* species, *B. xylanisolvens* DSM 23964, has been approved for supplementation of pasteurized milk products under Novel Food Regulation No. 258/97 by the European Commission (Brodmann et al. 2017). But only inactivated cells of *B. xylanisolvens* were allowed in the final product (EFSA Panel on Dietetic Products and Nutrition and Allergies 2015). This phenomenon can be attributed to the limited scientific reports on the safety assessment of

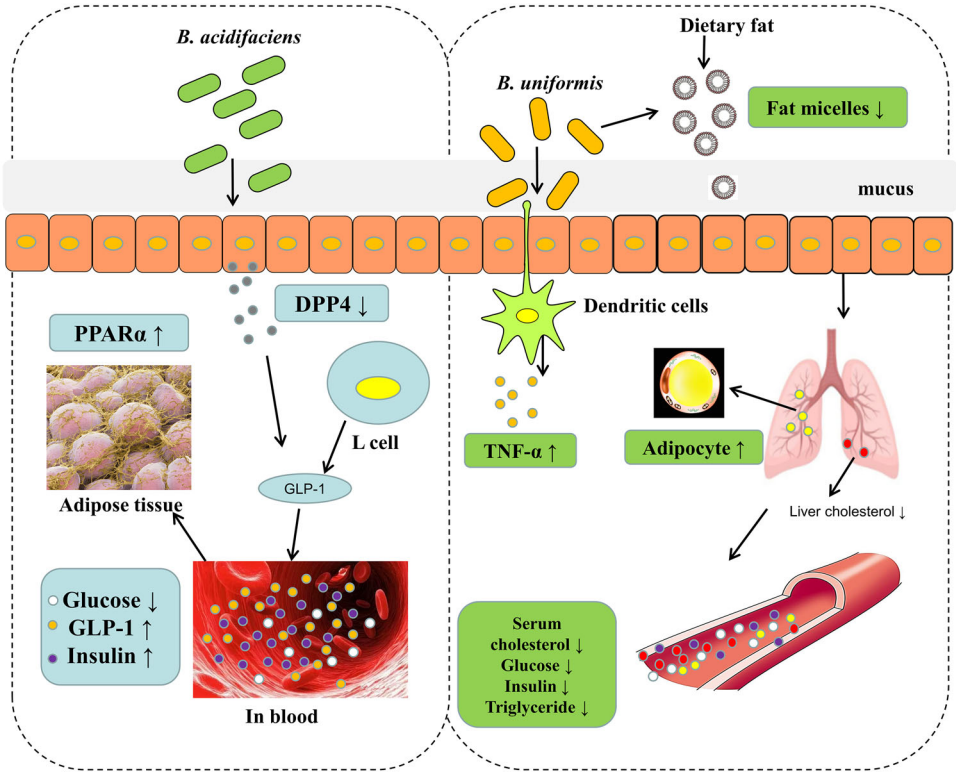

Figure 3. *B. acidifaciens* and *B. uniformis* regulate obesity-induced glucose intolerance in mice. Two gut commensal bacteria were to protect the host against obesity: (i) *B. acidifaciens* feeding resulted in activation of fat oxidation through the bile acid-TGR5-PPARα axis in adipose tissues, which may lead to high energy expenditure. *B. acidifaciens* activates DPP-4 in the gut and subsequently increases GLP-1, which may contribute to glucose homeostasis (Yang et al. 2017). (ii) The oral administration of *B. uniformis* CECT 7771 reduced body weight gain, liver steatosis, liver cholesterol, triglyceride concentrations and increased small adipocyte numbers in HFD-fed mice. The strain also reduced serum cholesterol, triglyceride, glucose, insulin and leptin levels and reduced number of fat micelles detected in enterocytes. Meanwhile, the administration of *B. uniformis* CECT 7771 increased TNF-α production and phagocytosis. Administering this strain also increased TNF-α production by dendritic cells in response to LPS stimulation, which was significantly reduced by HFD (Gauffin Cano et al. 2012).Note: DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; PPARα, peroxisome proliferator-activated receptor α; TNF-α, Tumor necrosis factor-α.

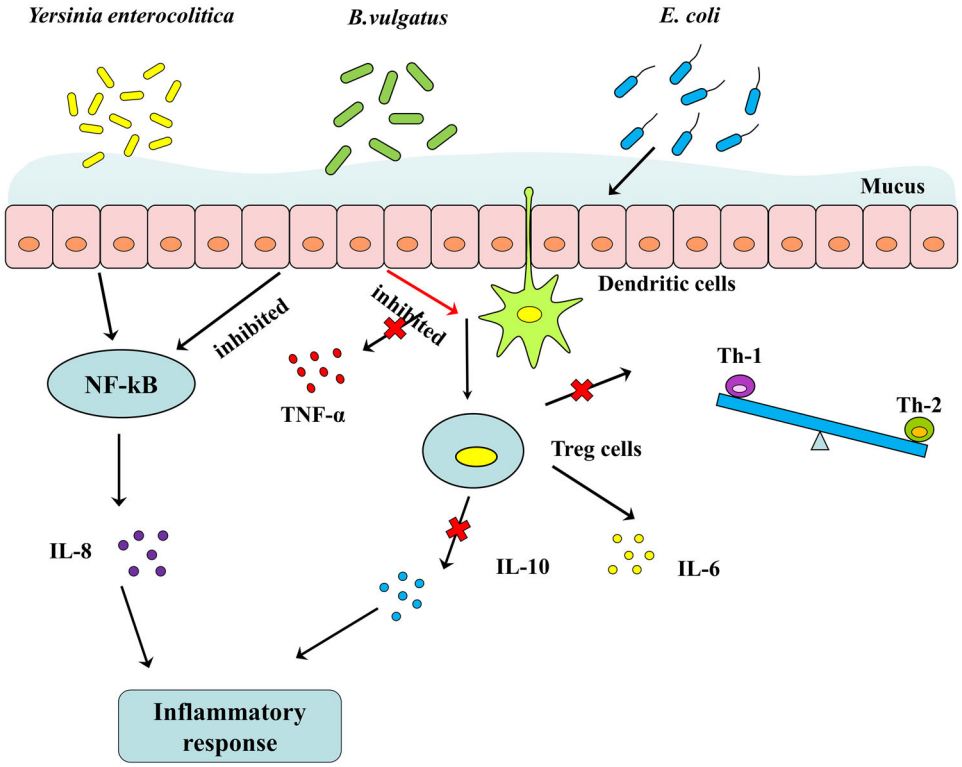

Figure 4. *B. vulgatus* involves in tissue inflammatory inhibition and immune homeostasis. (i) *B. vulgatus* mpk can inhibit the *Y. enterocolitica*-induced NF-κB activation and IL-8 production (Frick et al. 2007). (ii) *B. vulgatus* mpk protects against *E. coli*-induced Colitis by reducing the expression of TNF-α, IL-10, decreased Th1 polarization. (iii) *B. vulgatus* mpk prevent colitis by inducing semi-mature dendritic cells along with the accumulation of IL-6-secreting dendritic cells in the intestine, reducing their migration to mesenteric lymph nodes, and reducing T cell activation (Frick et al. 2006). Note: NF-κB, nuclear factor-kappa B.

Bacteroides species. Thus, it is necessary to perform a comprehensive safety evaluation of *Bacteroides* to rationally use them under the premise of avoiding their pathogenicity.

A recent review (Saarela 2019) indicated that the assessment of the NGP should include (i) correct identification of the strain, (ii) whole genome sequence based analysis of safety and confirmation of the identity, (iii) regulatory issues, (iv) growth experiments, (v) in vitro tests for safety, (vi) up-scaling of the production to a pilot scale fermentors and downstream processing, storage stability, (vii) animal and human studies. We suggest that more factors should be considered, such as the production of specific metabolites, the interaction between different *Bacteroides* species with the pathogenic bacteria, and the detection of potential virulence factors.

Prospects

Although a series of studies considered the *Bacteroides* species as one of candidates of NGP, the role of different *Bacteroides* species in human health and diseases finally has been demonstrated to be controversial. We proposed that only a part of *Bacteroides* strains, such as *B. fragilis* NCTC 9343 and *B. xylanisolvens* DSM 23964, have the potential to be used as the candidates of the NGP. More studies are required to verify the safety and efficacy of the other *Bacteroides* strains for the future application as probiotics. Thus, the reasonable separation and selection standard of probiotic *Bacteroides* should be established. Besides, because of the complex relationship between *Bacteroides* and host, there are some problems need to be addressed:

i. The functional analysis, safety evaluation, and clinical evaluation of *Bacteroides* are the basis for the selection of probiotics. However, to date, the safety evaluation of *Bacteroides* is limited to that of *B. fragilis* (Wang et al. 2017), *B. uniformis* (Fernández-Murga and Sanz 2016), and *B. xylanisolvens* (Ulsemer et al. 2012a, 2012b, 2012c). Moreover, concern remains regarding their source, culture history, phenotype, genotype, and resistance acquisition, and few clinical trials have been conducted to evaluate their safety. Notably, *B. xylanisolvens* DSM 23964 is the first *Bacteroides* strain approved by the European commission for use in food production after a thorough evaluation involving *in vitro* and *in vivo* safety tests and clinical evaluation. Thus, it is necessary to extend these safety evaluation techniques to other *Bacteroides* species.
ii. As *Bacteroides* species are strictly anaerobic, long-term exposure to air may reduce their viability. Therefore, it's a challenge to find suitable industrial processing and packaging methods to ensure their optimal biological activity and to maintain over a long duration. Recent studies have shown that supplying *B. xylanisolvens* DSM 23964 in the form of fermented or frozen foods or in a powder form may help to maintain the beneficial properties of the metabolites produced by the strain and to prolong the shelf life of the product (Ulsemer et al. 2012a).
iii. Furthermore, effective dietary complementation to enhance growth and colonization in the intestinal tract would maximize its probiotic effects. Notably, studies have shown that dietary nutrition is the main factor in the structure and function of the intestinal microbiome (Murphy et al. 2010; Carmody et al. 2015) and that changes in the gut microbiota composition may affect the host's metabolic status. One study found that the type of polysaccharide available guides the diet-induced alterations in the composition of intestinal *Bacteroides* species (Sonnenburg et al. 2010). This finding supports the need to optimize the rational use of *Bacteroides* probiotic function via enrichment of the desired probiotic *Bacteroides* strains.
iv. Recent studies by Zimmermann et al. (2019) and Vich Vila et al. (2020) indicated that specific *Bacteroides* strains such as *B. thetaiotaomicron* and *B. dorei* could encode enzymes to affect the systemic drug metabolism in mice. Thus, it is necessary to understand the mechanistically connection between *Bacteroides* species and interpersonal variation in drug metabolism.
v. Recently, a study showed that *B. fragilis* can inhibit the colonization of *V. parahaemolyticus* (Li et al. 2017), suggesting a tight interaction between *Bacteroides* species and other members of intestinal microbial community in the intestine. Thus, enhancing the analysis of these interactions is conducive for the reasonable utilization of *Bacteroides* in alleviating disease.

In summary, we discuss the existing knowledge about the impact of *Bacteroides* in host health and diseases, and suggest further attention should focus on the screening and safety assessment of *Bacteroides* as well as the interaction between *Bacteroides* and other gut microbes, dietary factors, and drugs.

Disclosure statement

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ORCID

Yuan-Kun Lee http://orcid.org/0000-0002-3884-4706

References

Agarwal, N., D. R. Hansberry, and I. M. Goldstein. 2014. Infection with *Bacteroides thetaiotaomicron* during posterior decompression and dynamic stabilization of the lumbar spine: A case report and review of the literature. *The International Journal of Neuroscience* 124 (8):621–5. doi: 10.3109/00207454.2013.865618.

Allan, S. E., R. Broady, S. Gregori, M. E. Himmel, N. Locke, M. G. Roncarolo, R. Bacchetta, and M. K. Levings. 2008. $CD4^+$ T-regulatory cells: Toward therapy for human diseases. *Immunological Reviews* 223:391–421. doi: 10.1111/j.1600-065X.2008.00634.x.

Bäckhed, F., H. Ding, T. Wang, L. V. Hooper, G. Y. Koh, A. Nagy, C. F. Semenkovich, and J. I. Gordon. 2004. The gut microbiota as an environmental factor that regulates fat storage. *Proceedings of the National Academy of Sciences of the United States of America* 101 (44):15718–23. doi: 10.1073/pnas.0407076101.

Bakir, M. A., M. Kitahara, M. Sakamoto, M. Matsumoto, and Y. Benno. 2006a. *Bacteroides finegoldii* sp nov. isolated from human faeces. *International Journal of Systematic and Evolutionary Microbiology* 56 (5):931–5. doi: 10.1099/ijs.0.64084-0.

Bakir, M. A., M. Kitahara, M. Sakamoto, M. Matsumoto, and Y. Benno. 2006b. *Bacteroides intestinalis* sp. nov. isolated from human faeces. *International Journal of Systematic and Evolutionary Microbiology* 56 (1):151–4. doi: 10.1099/ijs.0.63914-0.

Bakir, M. A., M. Sakamoto, M. Kitahara, M. Matsumoto, and Y. Benno. 2006c. *Bacteroides dorei* sp. nov., isolated from human faeces. *International Journal of Systematic and Evolutionary Microbiology* 56 (Pt 7):1639–43. doi: 10.1099/ijs.0.64257-0.

Bamba, T., H. Matsuda, M. Endo, and Y. Fujiyama. 1995. The pathogenic role of *Bacteroides vulgatus* in patients with ulcerative colitis. *Journal of Gastroenterology* 30 (Suppl 8):45–7.

Basset, C., J. Holton, A. Bazeos, D. Vaira, and S. Bloom. 2004. *Arehelicobacter* species and enterotoxigenic *Bacteroides fragilis* involved in inflammatory bowel disease? *Digestive Diseases and Sciences* 49 (9):1425–32. doi: 10.1023/B:DDAS.0000042241.13489.88.

Baughn, A. D., and M. H. Malamy. 2004. The strict anaerobe *Bacteroides fragilis* grows in and benefits from nanomolar concentrations of oxygen. *Nature* 427 (6973):441–4. doi: 10.1038/nature02285.

Bäumler, A. J., and V. Sperandio. 2016. Interactions between the microbiota and pathogenic bacteria in the gut. *Nature* 535 (7610): 85–93. doi: 10.1038/nature18849.

Belkacemi, S., N. Cassir, J. Delerce, F. Cadoret, and B. L. Scola. 2018. 'Bacteroides cutis,' a new bacterial species isolated from human skin. *New Microbes and New Infections* 22:17–8. doi: 10.1016/j.nmni.2017.12.007.

Belunis, C. J., T. Clementz, S. M. Carty, and C. R. Raetz. 1995. Inhibition of lipopolysaccharide biosynthesis and cell growth following inactivation of the kdtA gene in *Escherichia coli*. *The Journal of Biological Chemistry* 270 (46):27646–52. doi: 10.1074/jbc.270.46.27646.

Benítez-Páez, A., E. M. Gómez del Pulgar, and Y. Sanz. 2017. The glycolytic versatility of *Bacteroides uniformis* CECT 7771 and its genome response to oligo and polysaccharides. *Frontiers in Cellular and Infection Microbiology* 7:383. doi: 10.3389/fcimb.2017.00383.

Benno, Y., J. Watabe, and T. Mitsuoka. 1983. *Bacteroides pyogenes* sp. nov. *Bacteroides suis* sp. nov. and *Bacteroides helcogenes* sp. nov. new species from abscesses and feces of pigs. *Systematic and Applied Microbiology* 4 (3):396–407. doi: 10.1016/S0723-2020(83)80024-1.

Bloom, S. M., V. N. Bijanki, G. M. Nava, L. L. Sun, N. P. Malvin, D. L. Donermeyer, W. Michael Dunne, P. M. Allen, and T. S. Stappenbec. 2011. Commensal *Bacteroides* species induce colitis in host-genotype-specific fashion in a mouse model of inflammatory bowel disease. *Cell Host Microbe* 9 (5):390–403. doi: 10.1016/j.chom.2011.04.009.

Bogdan, M., V. Zujić Atalić, I. Hećimović, and D. Vuković. 2015. Brain abscess due to *Aggregatibacter aphrophilus* and *Bacteroides uniformis*. *Acta Medica Academica* 44 (2):181–5. doi: 10.5644/ama2006-124.144.

Brodmann, T., A. Endo, M. Gueimonde, G. Vinderola, W. Kneifel, W. M. de Vos, S. Salminen, and C. Gómez-Gallego. 2017. Safety of novel microbes for human consumption: Practical examples of assessment in the European Union. *Frontiers in Microbiology* 8:1725. doi: 10.3389/fmicb.2017.01725.

Brook, I. 1990. The clinical importance of all members of the *Bacteroides fragilis* group. *J. Antimicrob. Chemother* 25 (3):473–4. doi: 10.1093/jac/25.3.473.

Cani, P. D., J. Amar, M. A. Iglesias, M. Poggi, C. Knauf, D. Bastelica, A. M. Neyrinck, F. Fava, K. M. Tuohy, C. Chabo, et al. 2007. Metabolic endotoxemia initiates obesity and insulin resistance. *Diabetes* 56 (7):1761–72. doi: 10.2337/db06-1491.

Carmody, R. N., G. K. Gerber, J. M. Luevano, Jr, D. M. Gatti, L. Somes, K. L. Svenson, and P. J. Turnbaugh. 2015. Diet dominates host genotype in shaping the murine gut microbiota. *Cell Host & Microbe* 17 (1):72–84. doi: 10.1016/j.chom.2014.11.010.

Cassir, N., O. Croce, I. Pagnier, S. Benamar, C. Couderc, C. Robert, D. Raoult, and B. La Scola. 2014. Non-contiguous finished genome sequence and description of *Bacteroides neonati* sp. nov., a new species of anaerobic bacterium. *Standards in Genomic Sciences* 9 (3): 794–806. doi: 10.4056/sigs.5159098.

Chassard, C., E. Delmas, P. A. Lawson, and A. Bernalier-Donadille. 2008. *Bacteroides xylanisolvens* sp. nov., a xylan-degrading bacterium isolated from human faeces . *International Journal of Systematic and Evolutionary Microbiology* 58 (Pt 4):1008–13. doi: 10.1099/ijs.0.65504-0.

Chow, A. W., and L. B. Guze. 1974. Bacteroidaceae bacteremia: Clinical experience with 112 patients. *Medicine* 53 (2):93–126. doi: 10.1097/00005792-197403000-00001.

Clavel, T., A. Saalfrank, C. Charrier, and D. Haller. 2010. Isolation of bacteria from mouse caecal samples and description of *Bacteroides sartorii* sp. nov. *Archives of Microbiology* 192 (6):427–35. doi: 10.1007/s00203-010-0568-6.

Conte, M. P., S. Schippa, I. Zamboni, M. Penta, F. Chiarini, L. Seganti, J. Osborn, P. Falconieri, O. Borrelli, and S. Cucchiara. 2006. Gut-associated bacterial microbiota in paediatric patients with inflammatory bowel disease. *Gut* 55 (12):1760–7. doi: 10.1136/gut.2005.078824.

Corzo, G., and S. E. Gilliland. 1999. Measurement of bile salt hydrolase activity from *Lactobacillus acidophilus* based on disappearance of conjugated bile salts. *Journal of Dairy Science* 82 (3):466–71. doi: 10.3168/jds.S0022-0302(99)75255-0.

Cruz-Bravo, R. K., R. G. Guevara-González, M. Ramos-Gómez, B. D. Oomah, P. Wiersma, R. Campos-Vega, and G. Loarca-Piña. 2014. The fermented non-digestible fraction of common bean (*Phaseolus vulgaris* L.) triggers cell cycle arrest and apoptosis in human colon adenocarcinoma cells. *Genes & Nutrition* 9 (1):359. doi: 10.1007/s12263-013-0359-1.

Curtis, M. M., Z. Hu, C. Klimko, S. Narayanan, R. Deberardinis, and V. Sperandio. 2014. The gut commensal *Bacteroides thetaiotaomicron* exacerbates enteric infection through modification of the metabolic landscape. *Cell Host Microbe* 16 (6):759–69. doi: 10.1016/j.chom.2014.11.005.

Deng, H., Z. Li, Y. Tan, Z. Guo, Y. Liu, Y. Wang, Y. Yuan, R. Yang, Y. Bi, Y. Bai, et al. 2016. A novel strain of *Bacteroides fragilis* enhances phagocytosis and polarises m1 macrophages. *Scientific Reports* 6: 29401. doi: 10.1038/srep29401.

Despres, J., E. Forano, P. Lepercq, S. Comtet-Marre, G. Jubelin, C. Chambon, C. J. Yeoman, M. E. Berg Miller, C. J. Fields, E. Martens, et al. 2016. Xylan degradation by the human gut *Bacteroides xylanisolvens* XB1A(T) involves two distinct gene clusters that are linked at the transcriptional level. *BMC Genomics* 17 (1):326. doi: 10.1186/s12864-016-2680-8.

Edwards, L. A., M. Lucas, E. A. Edwards, F. Torrente, R. B. Heuschkel, N. J. Klein, S. H. Murch, M. Bajaj-Elliott, and A. D. Phillips. 2011. Aberrant response to commensal *Bacteroides thetaiotaomicron* in Crohn's disease: An ex vivo human organ culture study. *Inflammatory Bowel Diseases*17 (5):1201–8. doi: 10.1002/ibd.21501.

EFSA Panel on Dietetic Products, Nutrition and Allergies. 2015. Scientific opinion on the safety of 'heat-treated milk products fermented with *Bacteroides xylanisolvens* DSM 23964' as a novel food. *EFSA Journal* 13:1–18. doi: 10.2903/j.efsa.2015.3956.

Eggerth, A. H., and B. H. Gagnon. 1933. The *Bacteroides* of human feces. *Journal of Bacteriology* 25 (4):389–413. doi: 10.1002/path.1700380110.

Elamin, E. E., A. A. Masclee, J. Dekker, H.-J. Pieters, and D. M. Jonkers. 2013. Short-chain fatty acids activate AMP-activated protein kinase and ameliorate ethanol-induced intestinal barrier dysfunction in Caco-2 cell monolayers. *The Journal of Nutrition* 143 (12): 1872–81. doi: 10.3945/jn.113.179549.

Everard, A., C. Belzer, L. Geurts, J. P. Ouwerkerk, C. Druart, L. B. Bindels, Y. Guiot, M. Derrien, G. G. Muccioli, N. M. Delzenne, et al. 2013. 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* 110 (22):9066–71. doi: 10.1073/pnas.1219451110.

Faith, J. J., J. L. Guruge, M. Charbonneau, S. Subramanian, H. Seedorf, A. L. Goodman, J. C. Clemente, R. Knight, A. C. Heath, R. L. Leibel, et al. 2013. The long-term stability of the human gut microbiota. *Science (New York, N.Y.)* 341 (6141):1237439. doi: 10.1126/science.1237439.

Fan, H., Z. Chen, R. Lin, Y. Liu, X. Wu, S. Puthiyakunnon, Y. Wang, B. Zhu, Q. Zhang, Y. Bai, et al. 2019. *Bacteroides fragilis* strain ZY-312 defense against *Cronobacter sakazakii*-induced necrotizing enterocolitis *in vitro* and in a neonatal rat model. *mSystems* 4 (4): e00305. doi: 10.1128/mSystems.00305-19.

Farrar, M. D., T. R. Whitehead, J. Lan, P. Dilger, R. Thorpe, K. T. Holland, and S. R. Carding. 2005. Engineering of the gut commensal bacterium *Bacteroides ovatus* to produce and secrete biologically active murine interleukin-2 in response to xylan. *Journal of Applied Microbiology* 98 (5):1191–7. doi: 10.1111/j.1365-2672.2005.02565.x.

Fenner, L., V. Roux, M.-N. Mallet, and D. Raoult. 2005. *Bacteroides massiliensis* sp. nov., isolated from blood culture of a newborn. *International Journal of Systematic and Evolutionary Microbiology* 55 (Pt 3):1335–7. doi: 10.1099/ijs.0.63350-0.

Fernández-Murga, M. L., and Y. Sanz. 2016. Safety assessment of *Bacteroides uniformis* CECT 7771 isolated from stools of healthy breast-fed infants. *Plos One* 11 (1):e0145503. doi: 10.1371/journal.pone.0145503.

Feuillet, L., J. Carvajal, I. Sudre, J. Pelletier, J. M. Thomassin, M. Drancourt, and A. A. Cherif. 2005. First isolation of *Bacteroides thetaiotaomicron* from a patient with a cholesteatoma and experiencing meningitis. *J. Clin. Microbiol* 43 (3):1467–9. doi: 10.1128/JCM.43.3.1467-1469.2005.

Fonkou, M. D. M., A. Morand, P.-E. Fournier, D. Raoult, and G. Dubourg. 2017. 'Bacteroides ihuae' sp. nov., a new bacterial species isolated from the human respiratory microbiome. *New Microbes and New Infections* 17:52–3. doi: 10.1016/j.nmni.2017.01.011.

Freitas, M., E. Tavan, K. Thoreux, C. Cayuela, C. Sapin, and G. Trugnan. 2003. *Lactobacillus casei* DN-114 001 and *Bacteroides thetaitaomicrom* VPI-5482 inhibit rotavirus infection by modulating apical glycosylation pattern of cultured human intestinal HT29-MTX cells. *Gastroenterology* 124 (4):A475–6. doi: 10.1016/S0016-5085(03)82406-X.

Frick, J. S., K. Fink, F. Kahl, M. J. Niemiec, M. Quitadamo, K. Schenk, and I. B. Autenrieth. 2007. Identification of commensal bacterial strains that modulate *Yersinia enterocolitica* and dextran sodium sulfate-induced inflammatory responses: Implications for the development of probiotics. *Infection and Immunity* 75 (7):3490–7. doi: 10.1128/IAI.00119-07.

Frick, J. S., N. Zahir, M. Müller, F. Kahl, O. Bechtold, M. B. Lutz, C. J. Kirschning, J. Reimann, B. Jilge, E. Bohn, et al. 2006. Colitogenic and non-colitogenic commensal bacteria differentially trigger DC maturation and Th cell polarization: An important role for IL-6. *European Journal of Immunology* 36 (6):1537–47. doi: 10.1002/eji.200635840.

Fu, X., Z. Liu, C. Zhu, H. Mou, and Q. Kong. 2019. Nondigestible carbohydrates, butyrate, and butyrate-producing bacteria. *Critical Reviews in Food Science and Nutrition* 59 (sup1):S130–S52. doi: 10.1080/10408398.2018.1542587.

Fukuda, S., H. Toh, K. Hase, K. Oshima, Y. Nakanishi, K. Yoshimura, T. Tobe, J. M. Clarke, D. L. Topping, T. Suzuki, et al. 2011. *Bifidobacteria* can protect from enteropathogenic infection through production of acetate. *Nature* 469 (7331):543–7. doi: 10.1038/nature09646.

Galloway, S. M., and C. R. Raetz. 1990. A mutant of *Escherichia coli* defective in the first step of endotoxin biosynthesis. *The Journal of Biological Chemistry* 265 (11):6394–402.

García-Bayona, L., and L. E. Comstock. 2018. Bacterial antagonism in host-associated microbial communities. *Science* 361 (6408):eaat2456. doi: 10.1126/science.aat2456.

Gauffin Cano, P., A. Santacruz, Á. Moya, and Y. Sanz. 2012. *Bacteroides uniformis* CECT 7771 ameliorates metabolic and immunological dysfunction in mice with high-fat-diet induced obesity. *Plos One* 7 (7):e41079. doi: 10.1371/journal.pone.0041079.

Gérard, P., P. Lepercq, M. Leclerc, F. Gavini, P. Raibaud, and C. Juste. 2007. *Bacteroides* sp. strain D8, the first cholesterol-reducing bacterium isolated from human feces. *Applied and Environmental Microbiology* 73 (18):5742–9. doi: 10.1128/AEM.02806-06.

Guo, S., M. Nighot, R. Al-Sadi, T. Alhmoud, P. Nighot, and T. Y. Ma. 2015. Lipopolysaccharide regulation of intestinal tight junction permeability is mediated by TLR4 signal transduction pathway activation of FAK and MyD88. *Journal of Immunology (Baltimore, Md. : 1950)* 195 (10):4999–5010. doi: 10.4049/jimmunol.1402598.

Guo, S., R. Al-Sadi, H. M. Said, and T. Y. Ma. 2013. Lipopolysaccharide causes an increase in intestinal tight junction permeability *in vitro* and *in vivo* by inducing enterocyte membrane expression and localization of TLR-4 and CD14. *The American Journal of Pathology* 182 (2):375–87. doi: 10.1016/j.ajpath.2012.10.014.

Hamady, Z. Z. R., N. Scott, M. D. Farrar, J. P. A. Lodge, K. T. Holland, T. Whitehead, and S. R. Carding. 2010. Xylan-regulated delivery of human keratinocyte growth factor-2 to the inflamed colon by the human anaerobic commensal bacterium Bacteroides ovatus. *Gut* 59 (4):461–9. doi: 10.1136/gut.2008.176131.

Hamady, Z. Z. R., N. Scott, M. D. Farrar, M. Wadhwa, P. Dilger, T. R. Whitehead, R. Thorpe, K. T. Holland, J. P. A. Lodge, and S. R. Carding. 2011. Treatment of colitis with a commensal gut bacterium engineered to secrete human TGF-β1 under the control of dietary xylan 1. *Inflammatory Bowel Diseases* 17 (9):1925–35. doi: 10.1002/ibd.21565.

Hansen, J. J., Y. Huang, D. A. Peterson, J. I. Gordon, E. B. Chang, and R. B. Sartor. 2012. 47 chronic colitis in *Bacteroides thetaiotaomicron*-monoassociated HLA-B27 transgenic rats is associated with altered transcription of receptor and metabolic genes in luminal bacteria. *Gastroenterology* 142 (5):S-13. doi: 10.1016/S0016-5085(12)60047-X.

Hatamoto, M., M. Kaneshige, A. Nakamura, and T. Yamaguchi. 2014. *Bacteroides luti* sp. nov., an anaerobic, cellulolytic and xylanolytic bacterium isolated from methanogenic sludge. *International Journal of Systematic and Evolutionary Microbiology* 64 (Pt 5):1770–4. doi: 10.1099/ijs.0.056630-0.

Hayashi, H., K. Shibata, M. A. Bakir, M. Sakamoto, S. Tomita, and Y. Benno. 2007. *Bacteroides coprophilus* sp. nov., isolated from human faeces. *International Journal of Systematic and Evolutionary Microbiology* 57 (Pt 6):1323–6. doi: 10.1099/ijs.0.64979-0.

Hecht, A. L., B. W. Casterline, Z. M. Earley, Y. A. Goo, D. R. Goodlett, and J. B. Wardenburg. 2016. Strain competition restricts colonization of an enteric pathogen and prevents colitis. *EMBO Reports* 17 (9):1281–91. doi: 10.15252/embr.201642282.

Hedberg, M., L. Lindqvist, T. Bergman, and C. E. Nord. 1995. Purification and characterization of a new beta-lactamase from *Bacteroides uniformis*. *Antimicrobial Agents and Chemotherapy* 39 (7):1458–61. doi: 10.1128/AAC.39.7.1458.

Henderson, G., P. Ulsemer, U. Schöber, A. Löffler, C.-A. Alpert, M. Zimmermann-Kordmann, W. Reutter, U. Karsten, S. Goletz, and M. Blaut. 2011. Occurrence of the human tumor-specific antigen structure Galβ1-3GalNAcα- (Thomsen-Friedenreich) and related structures on gut bacteria: Prevalence, immunochemical analysis and structural confirmation . *Glycobiology* 21 (10):1277–89. doi: 10.1093/glycob/cwr058.

Hochart-Behra, A.-C., H. Drobecq, M. Tourret, L. Dubreuil, and J. Behra-Miellet. 2014. Anti-stress proteins produced by *Bacteroides thetaiotaomicron* after nutrient starvation. *Anaerobe* 28:18–23. doi: 10.1016/j.anaerobe.2014.04.008.

Höffler, U. 1987. Anaerobic bacteria in human medicine. *Labmedica* 4: 21–6.

Holdeman, L. V., and W. E. C. Moore. 1974. New genus, *Coprococcus*, twelve new species, and emended descriptions of four previously described species of bacteria from human feces. *International Journal of Systematic Bacteriology* 24 (2):260–77. doi: 10.1099/00207713-24-2-260.

Holland, J. W., E. O. Hill, and W. A. Altemeier. 1977. Numbers and types of anaerobic bacteria isolated from clinical specimens since 1960. *Journal of Clinical Microbiology* 5 (1):20–5.

Hooper, L. V., M. H. Wong, A. Thelin, L. Hansson, P. G. Falk, and J. I. Gordon. 2001. Molecular analysis of commensal host-microbial relationships in the intestine. *Science (New York, N.Y.)* 291 (5505): 881–4. doi: 10.1126/science.291.5505.881.

Hsiao, E. Y., S. W. McBride, S. Hsien, G. Sharon, E. R. Hyde, T. McCue, J. A. Codelli, J. Chow, S. E. Reisman, J. F. Petrosino, et al. 2013. Microbiota modulate behavioral and physiological abnormalities associated with neurodevelopmental disorders. *Cell* 155 (7): 1451–63. doi: 10.1016/j.cell.2013.11.024.

Hudcovic, T., H. Kozáková, J. Kolínská, R. Stepánková, T. Hrncír, and H. Tlaskalová-Hogenová. 2009. Monocolonization with *Bacteroides ovatus* protects immunodeficient SCID mice from mortality in chronic intestinal inflammation caused by long-lasting dextran sodium sulfate treatment. *Physiological Research* 58 (1):101–10. doi: 10.1016/j.biologicals.2005.12.002.

Hwang, S., C. G. Lee, M. Jo, C. O. Park, S.-Y. Gwon, S. Hwang, H. C. Yi, S.-Y. Lee, Y.-B. Eom, B. Karim, et al. 2020. Enterotoxigenic *Bacteroides fragilis* infection exacerbates tumorigenesis in AOM/DSS mouse model. *International Journal of Medical Sciences* 17 (2): 145–52. doi: 10.7150/ijms.38371.

Irisawa, T., Saputra, S. M. Kitahara, M. Sakamoto, Sulistiani, T. Yulineri, A. Dinoto, and M. Ohkuma. 2016. *Bacteroides caecicola* sp. nov. and *Bacteroides gallinaceum* sp. nov., isolated from the caecum of an indonesian chicken. *International Journal of Systematic and Evolutionary Microbiology* 66 (3):1431–7. doi: 10.1099/ijsem.0.000899.

Jensen, N. S., and E. Canale-Parola. 1986. *Bacteroides pectinophilus* sp. nov. and *Bacteroides galacturonicus* sp. nov.: Two pectinolytic bacteria from the human intestinal tract. *Applied and Environmental Microbiology* 52 (4):880–7. doi: 10.1128/AEM.52.4.880-887.1986.

Johnson, J. L., W. E. C. Moore, and L. V. H. Moore. 1986. *Bacteroides caccae* sp. nov., *Bacteroides merdae* sp. nov., and *Bacteroides stercoris* sp. nov. isolated from human feces. *International Journal of Systematic Bacteriology* 36 (4):499–501. doi: 10.1099/00207713-36-4-499.

Kato, N., C. X. Liu, H. Kato, K. Watanabe, Y. Tanaka, T. Yamamoto, K. Suzuki, and K. Ueno. 2000. A new subtype of the metalloprotease toxin gene and the incidence of the three *bft* subtypes among *Bacteroides fragilis* isolates in Japan. *FEMS Microbiology Letters* 182 (1):171–6. doi: 10.1111/j.1574-6968.2000.tb08892.x.

Kelly, D., J. I. Campbell, T. P. King, G. Grant, E. A. Jansson, A. G. P. Coutts, S. Pettersson, and S. Conway. 2004. Commensal anaerobic gut bacteria attenuate inflammation by regulating nuclear-cytoplasmic shuttling of PPAR-gamma and RelA . *Nature Immunology* 5 (1):104–12. doi: 10.1038/ni1018.

Kim, J. M., S. J. Cho, Y.-K. Oh, H.-Y. Jung, Y.-J. Kim, and N. Kim. 2002. Nuclear factor-kappa B activation pathway in intestinal epithelial cells is a major regulator of chemokine gene expression and neutrophil migration induced by *Bacteroides fragilis* enterotoxin. *Clinical and Experimental Immunology* 130 (1):59–66. doi: 10.1046/j.1365-2249.2002.01921.x.

Kim, M. G., J. W. Jeon, I. H. Ryu, J. J. Lee, J. S. Kim, J. W. Choi, B.-S. Cho, and H. J. Yoon. 2014. Mycotic abdominal aortic aneurysm caused by *Bacteroides thetaiotaomicron* and *Acinetobacter lwoffii*: The first case in Korea. *Infection & Chemotherapy* 46 (1):54–8. doi: 10.3947/ic.2014.46.1.54.

Kim, M.-S., S. W. Roh, and J.-W. Bae. 2010. *Bacteroides faecis* sp. nov., isolated from human faeces. *International Journal of Systematic and Evolutionary Microbiology* 60 (Pt 11):2572–6. doi: 10.1099/ijs.0.020024-0.

Kishi, D., I. Takahashi, Y. Kai, H. Tamagawa, H. Iijima, S. Obunai, R. Nezu, T. Ito, H. Matsuda, and H. Kiyono. 2000. Alteration of V beta usage and cytokine production of $CD4^+$ TCR beta beta homodimer T cells by elimination of *Bacteroides vulgatus* prevents colitis in TCR alpha-chain-deficient mice. *Journal of Immunology (Baltimore, Md. : 1950)* 165 (10):5891–9. doi: 10.4049/jimmunol.165.10.5891.

Kitahara, M., M. Sakamoto, M. Ike, S. Sakata, and Y. Benno. 2005. *Bacteroides plebeius* sp. nov. and Bacteroides coprocola sp. nov., isolated from human faeces. *International Journal of Systematic and Evolutionary Microbiology* 55 (Pt 5):2143–7. doi: 10.1099/ijs.0.63788-0.

Kitahara, M., M. Sakamoto, S. Tsuchida, K. Kawasumi, H. Amao, Y. Benno, and M. Ohkuma. 2012. *Bacteroides stercorirosoris* sp. nov. and *Bacteroides faecichinchillae* sp. nov., isolated from chinchilla (Chinchilla lanigera) faeces. *International Journal of Systematic and Evolutionary Microbiology* 62 (Pt 5):1145–50. doi: 10.1099/ijs.0.032706-0.

Kitahara, M., S. Tsuchida, K. Kawasumi, H. Amao, M. Sakamoto, Y. Benno, and M. Ohkuma. 2011. *Bacteroides chinchillae* sp. nov. and *Bacteroides rodentium* sp. nov., isolated from chinchilla (*Chinchilla lanigera*) faeces. *International Journal of Systematic and Evolutionary Microbiology* 61 (Pt 4):877–81. doi: 10.1099/ijs.0.024026-0.

Krinos, C. M., M. J. Coyne, K. G. Weinacht, A. O. Tzianabos, D. L. Kasper, and L. E. Comstock. 2001. Extensive surface diversity of a commensal microorganism by multiple DNA inversions. *Nature* 414 (6863):555–8. doi: 10.1038/35107092.

Lagkouvardos, I., R. Pukall, B. Abt, B. U. Foesel, J. P. Meier-Kolthoff, N. Kumar, A. Bresciani, I. Martínez, S. Just, C. Ziegler, et al. 2016. The mouse intestinal bacterial collection (miBC) provides host-specific insight into cultured diversity and functional potential of the gut microbiota. *Nature Microbiology* 1 (10):16131. doi: 10.1038/nmicrobiol.2016.131.

Lan, P. T. N., M. Sakamoto, S. Sakata, and Y. Benno. 2006. *Bacteroides barnesiae* sp. nov., *Bacteroides salanitronis* sp. nov. and *Bacteroides gallinarum* sp. nov., isolated from chicken caecum. *International Journal of Systematic and Evolutionary Microbiology* 56 (12):2853–9. doi: 10.1099/ijs.0.64517-0.

Ley, R. E., M. Hamady, C. Lozupone, P. J. Turnbaugh, R. R. Ramey, J. S. Bircher, M. L. Schlegel, T. A. Tucker, M. D. Schrenzel, R. Knight, et al. 2008. Evolution of mammals and their gut microbes. *Science (New York, N.Y.)* 320 (5883):1647–51. doi: 10.1126/science.1155725.

Li, J., G. Mandal, and B. P. Rosen. 2016. Expression of arsenic resistance genes in the obligate anaerobe *Bacteroides vulgatus* ATCC 8482, a gut microbiome bacterium. *Anaerobe* 39:117–23. doi: 10.1016/j.anaerobe.2016.03.012.

Li, Z., H. Deng, Y. Zhou, Y. Tan, X. Wang, Y. Han, Y. Liu, Y. Wang, R. Yang, Y. Bi, et al. 2017. Bioluminescence imaging to track *Bacteroides fragilis* inhibition of *Vibrio parahaemolyticus* infection in mice. *Frontiers in Cellular and Infection Microbiology* 7:170. doi: 10.3389/fcimb.2017.00170.

Liu, R., J. Hong, X. Xu, Q. Feng, D. Zhang, Y. Gu, J. Shi, S. Zhao, W. Liu, X. Wang, et al. 2017. Gut microbiome and serum metabolome alterations in obesity and after weight-loss intervention. *Nature Medicine* 23 (7):859–68. doi: 10.1038/nm.4358.

Lucke, K., S. Miehlke, E. Jacobs, and M. Schuppler. 2006. Prevalence of *Bacteroides* and *Prevotella* spp. in ulcerative colitis. *Journal of Medical Microbiology* 55 (Pt 5):617–24. doi: 10.1099/jmm.0.46198-0.

Maeda, H., H. Umezawa, M. Goshima, T. Hattori, T. Nakamura, T. Umeda, and M. Shiono. 2011. Primary infected abdominal aortic aneurysm: Surgical procedures, early mortality rates, and a survey of the prevalence of infectious organisms over a 30-year period. *Surgery Today* 41 (3):346–51. doi: 10.1007/s00595-010-4279-z.

Mailhe, M., D. Ricaboni, V. Vitton, P.-E. Fournier, S. Khelaifia, and D. Raoult. 2016. *Bacteroides mediterraneensis*" sp. nov. a new human-

associated bacterium isolated from ileum specimen. *New Microbes and New Infections* 13:48–50. doi: 10.1016/j.nmni.2016.06.003.

Mancuso, G., A. Midiri, C. Biondo, C. Beninati, M. Gambuzza, D. Macrì, A. Bellantoni, A. Weintraub, T. Espevik, and G. Teti. 2005. *Bacteroides fragilis*-derived lipopolysaccharide produces cell activation and lethal toxicity via toll-like receptor 4. *Infection and Immunity* 73 (9):5620–7. doi: 10.1128/IAI.73.9.5620-5627.2005.

Masoudi, A., C. R. H. Raetz, P. Zhou, and C. W. Pemble. 2014. Chasing acyl carrier protein through a catalytic cycle of lipid a production. *Nature* 505 (7483):422–6. doi: 10.1038/nature12679.

Matsuda, H., Y. Fujiyama, A. Andoh, T. Ushijima, T. Kajinami, and T. Bamba. 2000. Characterization of antibody responses against rectal mucosa-associated bacterial flora in patients with ulcerative colitis. *Journal of Gastroenterology and Hepatology* 15 (1):61–8. doi: 10.1046/j.1440-1746.2000.02045.x.

Mazmanian, S. K., C. H. Liu, A. O. Tzianabos, and D. L. Kasper. 2005. An immunomodulatory molecule of symbiotic bacteria directs maturation of the host immune system. *Cell* 122 (1):107–18. doi: 10.1016/j.cell.2005.05.007.

Mazmanian, S. K., J. L. Round, and D. L. Kasper. 2008. A microbial symbiosis factor prevents intestinal inflammatory disease. *Nature* 453 (7195):620–5. doi: 10.1038/nature07008.

Meehan, B. M., A. D. Baughn, R. Gallegos, and M. H. Malamy. 2012. Inactivation of a single gene enables microaerobic growth of the obligate anaerobe *Bacteroides fragilis*. *Proceedings of the National Academy of Sciences of the United States of America* 109 (30): 12153–8. doi: 10.1073/pnas.1203796109.

Meiselmikolajczyk, F., A. Rokosz, K. Kot, E. Zawidzka, C. Malchar, M. Nowaczyk, and A. Górski. 2003. Influence of clindamycin, metronidazole and polymyxin B on the expression of cell adhesion molecules stimulated by endotoxin and enterotoxin of *Bacteroides fragilis*. *Acta Microbiologica Polonica* 52 (4):361–72.

Messina, M., W. Mccaskill-Stevens, and J. W. Lampe. 2006. Addressing the soy and breast cancer relationship: Review, commentary, and workshop proceedings. *Journal of the National Cancer Institute* 98 (18):1275–84. doi: 10.1093/jnci/djj356.

Miragliotta, G., T. D. Gaudio, E. Tajani, and A. Mosca. 2006. *Bacteroides thetaiotaomicron* in posthysterectomy infection. *Anaerobe* 12 (5–6):276–8. doi: 10.1016/j.anaerobe.2006.07.002.

Mirande, C., E. Kadlecikova, M. Matulova, P. Capek, A. Bernalier-Donadille, E. Forano, and C. Béra-Maillet. 2010. Dietary fibre degradation and fermentation by two xylanolytic bacteria *Bacteroides xylanisolvens* XB1A and Roseburia intestinalis XB6B4 from the human intestine. *Journal of Applied Microbiology* 109 (2): 451–60. doi: 10.1111/j.1365-2672.2010.04671.x.

Miyamoto, Y., and K. Itoh. 2000. *Bacteroides acidifaciens* sp. nov., isolated from the caecum of mice. *International Journal of Systematic and Evolutionary Microbiology* 50 (1):145–8. doi: 10.1099/00207713-50-1-145.

Moore, W. E., and L. V. Holdeman. 1974. Human fecal flora: The normal flora of 20 Japanese-Hawaiians. *Applied Microbiology* 27 (5): 961–79. doi: 10.1128/AEM.27.5.961-979.1974.

Murphy, E. F., P. D. Cotter, S. Healy, T. M. Marques, O. O'Sullivan, F. Fouhy, S. F. Clarke, P. W. O'Toole, E. M. Quigley, C. Stanton, et al. 2010. Composition and energy harvesting capacity of the gut microbiota: Relationship to diet, obesity and time in mouse models. *Gut* 59 (12):1635–42. doi: 10.1136/gut.2010.215665.

Myers, L. L., D. S. Shoop, L. L. Stackhouse, F. S. Newman, R. J. Flaherty, G. W. Letson, and R. B. Sack. 1987. Isolation of enterotoxigenic *Bacteroides fragilis* from humans with diarrhea. *Journal of Clinical Microbiology* 25 (12):2330–3. doi: 10.1128/JCM.25.12.2330-2333.1987.

Nakano, V., and M. J. Avila-Campos. 2004. Virulence markers and antimicrobial susceptibility of bacteria of the *Bacteroides fragilis* group isolated from stool of children with diarrhea in São Paulo, Brazil. *Memorias Do Instituto Oswaldo Cruz* 99 (3):307–12. doi:/S0074-02762004000300012. doi: 10.1590/s0074-02762004000300012.

Ndongo, S., M. L. Tall, I. I. Ngom, P.-E. Fournier, A. Levasseur, D. Raoult, and S. Khelaifia. 2019. Genome sequence and description of Bacteroides bouchesdurhonensis sp. nov., a new anaerobic bacterium isolated from the human gut. *New Microbes and New Infections* 31: 100571. doi: 10.1016/j.nmni.2019.100571.

Neef, A., and Y. Sanz. 2013. Future for probiotic science in functional food and dietary supplement development. *Current Opinion in Clinical Nutrition & Metabolic Care* 16 (6):679–87. doi: 10.1097/MCO.0b013e328365c258.

Nishiyama, T., A. Ueki, N. Kaku, K. Watanabe, and K. Ueki. 2009. *Bacteroides graminisolvens* sp. nov., a xylanolytic anaerobe isolated from a methanogenic reactor treating cattle waste. *International Journal of Systematic and Evolutionary Microbiology* 59 (Pt 8): 1901–7. doi: 10.1099/ijs.0.008268-0.

Obiso, R. J., A. O. Azghani, and T. D. Wilkins. 1997. The *Bacteroides fragilis* toxin fragilysin disrupts the paracellular barrier of epithelial cells. *Infection and Immunity* 65 (4):1431–9. doi: 10.1128/IAI.65.4.1431-1439.1997.

Ochoa-Repáraz, J., D. W. Mielcarz, Y. Wang, S. Begum-Haque, S. Dasgupta, D. L. Kasper, and L. H. Kasper. 2010. A polysaccharide from the human commensal *Bacteroides fragilis* protects against CNS demyelinating disease. *Mucosal Immunology* 3 (5):487–95. doi: 10.1038/mi.2010.29.

Ohkusa, T., T. Yoshida, N. Sato, S. Watanabe, H. Tajiri, and I. Okayasu. 2009. Commensal bacteria can enter colonic epithelial cells and induce proinflammatory cytokine secretion: A possible pathogenic mechanism of ulcerative colitis. *Journal of Medical Microbiology* 58 (Pt 5):535–45. doi: 10.1099/jmm.0.005801-0.

O'Toole, P. W., J. R. Marchesi, and C. Hill. 2017. Next-generation probiotics: The spectrum from probiotics to live biotherapeutics. *Nature Microbiology* 2:17057. doi: 10.1038/nmicrobiol.2017.57.

Ott, S. J., M. Musfeldt, D. F. Wenderoth, J. Hampe, O. Brant, U. R. Fölsch, K. N. Timmis, and S. Schreiber. 2004. Reduction in diversity of the colonic mucosa associated bacterial microflora in patients with active inflammatory bowel disease. *Gut* 53 (5):685–93. doi: 10.1136/gut.2003.025403.

Owen, C. G., R. M. Martin, P. H. Whincup, G. D. Smith, and D. G. Cook. 2005. Effect of infant feeding on the risk of obesity across the life course: A quantitative review of published evidence. *Pediatrics* 115 (5):1367–77. doi: 10.1542/peds.2004-1176.

Patrascu, O., F. Béguet-Crespel, L. Marinelli, E. L. Chatelier, A.-L. Abraham, M. Leclerc, C. Klopp, N. Terrapon, B. Henrissat, H. M. Blottière, et al. 2017. A fibrolytic potential in the human ileum mucosal microbiota revealed by functional metagenomic. *Scientific Reports* 7 (1):40248. doi: 10.1038/srep40248.

Patrick, S., K. L. Jobling, D. O'Connor, Z. Thacker, D. T. F. Dryden, and G. W. Blakely. 2011. A unique homologue of the eukaryotic protein-modifier ubiquitin present in the bacterium *Bacteroides fragilis*, a predominant resident of the human gastrointestinal tract. *Microbiology (Reading, England)* 157 (Pt 11):3071–8. doi: 10.1099/mic.0.049940-0.

Pierce, J. V., and H. D. Bernstein. 2016. Genomic diversity of enterotoxigenic strains of *Bacteroides fragilis*. *Plos One* 11 (6):e0158171. doi: 10.1371/journal.pone.0158171.

Porter, N. T., P. Canales, D. A. Peterson, and E. C. Martens. 2017. A subset of polysaccharide capsules in the human symbiont *Bacteroides thetaiotaomicron* promote increased competitive fitness in the mouse gut. *Cell Host Microbe* 22 (4):494–506. doi: 10.1016/j.chom.2017.08.020.

Prindiville, T. P., R. A. Sheikh, S. H. Cohen, Y. J. Tang, M. C. Cantrell, and J. Silva. Jr. 2000. *Bacteroides fragilis* enterotoxin gene sequences in patients with inflammatory bowel disease. *Emerging Infectious Diseases* 6 (2):171–4. doi: 10.3201/eid0602.000210.

Qian, C., and X. Cao. 2013. Regulation of Toll-like receptor signaling pathways in innate immune responses. *Annals of the New York Academy of Sciences* 1283 (1):67–74. doi: 10.1111/j.1749-6632.2012.06786.x.

Rabizadeh, S., K. -J. Rhee, S. Wu, D. Huso, C. M. Gan, J. E. Golub, X. Wu, M. Zhang, and C. L. Sears. 2007. Enterotoxigenic *Bacteroides fragilis*: A potential instigator of colitis. *Inflammatory Bowel Diseases* 13 (12):1475–83. doi: 10.1002/ibd.20265.

Ramakrishna, C., M. Kujawski, H. Chu, L. Li, S. K. Mazmanian, and E. M. Cantin. 2019. *Bacteroides fragilis* polysaccharide A induces IL-

10 secreting B and T cells that prevent viral encephalitis. *Nature Communications* 10 (1):2153. doi: 10.1038/s41467-019-09884-6.

Rath, H. C., H. H. Herfarth, J. S. Ikeda, W. B. Grenther, T. E. Hamm, Jr, E. Balish, J. D. Taurog, R. E. Hammer, K. H. Wilson, and R. B. Sartor. 1996. Normal luminal bacteria, especially *Bacteroides* species, mediate chronic colitis, gastritis, and arthritis in HLA-B27/human beta2 microglobulin transgenic rats. *Journal of Clinical Investigation* 98 (4):945–53. doi: 10.1172/JCI118878.

Rath, H. C., K. H. Wilson, and R. B. Sartor. 1999. Differential induction of colitis and gastritis in HLA-B27 transgenic rats selectively colonized with *Bacteroides vulgatus* or *Escherichia coli*. *Infection and Immunity* 67 (6):2969–74. doi: 10.1016/S0928-8244(99)00034-6.

Renouf, M., and S. Hendrich. 2011. *Bacteroides uniformis* is a putative bacterial species associated with the degradation of the isoflavone genistein in human feces. *The Journal of Nutrition* 141 (6):1120–6. doi: 10.3945/jn.111.140988.

Rhee, K.-J., S. Wu, X. Wu, D. L. Huso, B. Karim, A. A. Franco, S. Rabizadeh, J. E. Golub, L. E. Mathews, J. Shin, et al. 2009. Induction of persistent colitis by a human commensal, enterotoxigenic *Bacteroides fragilis*, in wild-type C57BL/6 mice. *Infection and Immunity* 77 (4):1708–18. doi: 10.1128/IAI.00814-08.

Robert, C., C. Chassard, P. A. Lawson, and A. Bernalier-Donadille. 2007. *Bacteroides cellulosilyticus* sp. nov., a cellulolytic bacterium from the human gut microbial community. *International Journal of Systematic and Evolutionary Microbiology* 57 (Pt 7):1516–20. doi: 10.1099/ijs.0.64998-0.

Rocha, E. R., and C. J. Smith. 2004. Transcriptional regulation of the *Bacteroides fragilis* ferritin gene (*ftnA*) by redox stress. *Microbiology (Reading, England)* 150 (Pt 7):2125–34. doi: 10.1099/mic.0.26948-0.

Rocha, E. R., and C. J. Smith. 2013. Ferritin-like family proteins in the anaerobe *Bacteroides fragilis*: When an oxygen storm is coming, take your iron to the shelter. *Biometals* 26 (4):577–91. doi: 10.1007/s10534-013-9650-2.

Round, J. L., and S. K. Mazmanian. 2010. Inducible Foxp3+ regulatory T-cell development by a commensal bacterium of the intestinal microbiota. *Proceedings of the National Academy of Sciences of the United States of America* 107 (27):12204–9. doi: 10.1073/pnas.0909122107.

Round, J. L., S. M. Lee, J. Li, G. Tran, B. Jabri, T. A. Chatila, and S. K. Mazmanian. 2011. The Toll-like receptor 2 pathway establishes colonization by a commensal of the human microbiota. *Science (New York, N.Y.)* 332 (6032):974–7. doi: 10.1126/science.1206095.

Rubtsov, Y. P., J. P. Rasmussen, E. Y. Chi, J. Fontenot, L. Castelli, X. Ye, P. Treuting, L. Siewe, A. Roers, W. R. Henderson, et al. 2008. Regulatory T cell-derived interleukin-10 limits inflammation at environmental interfaces. *Immunity* 28 (4):546–58. doi: 10.1016/j.immuni.2008.02.017.

Ruseler-van Embden, J. G., and H. C. Both-Patoir. 1983. Anaerobic gram-negative faecal flora in patients with Crohn's Disease and healthy subjects. *Antonie Van Leeuwenhoek International Leeuwenhoek* 49 (2):125–32. doi: 10.1007/BF00393670.

Saarela, M. H. 2019. Safety aspects of next generation probiotics. *Current Opinion in Food Science* 30:8–13. doi: 10.1016/j.cofs.2018.09.001.

Saitoh, S., S. Noda, Y. Aiba, A. Takagi, M. Sakamoto, Y. Benno, and Y. Koga. 2002. *Bacteroides ovatus* as the predominant commensal intestinal microbe causing a systemic antibody response in inflammatory bowel disease. *Clinical and Diagnostic Laboratory Immunology* 9 (1):54–9. doi: 10.1128/CDLI.9.1.54-59.2002.

Sakamoto, M., and M. Ohkuma. 2012. *Bacteroides sartorii* is an earlier heterotypic synonym of *Bacteroides chinchillae* and has priority. *International Journal of Systematic and Evolutionary Microbiology* 62 (Pt 6):1241–4. doi: 10.1099/ijs.0.035659-0.

Sakamoto, M., and M. Ohkuma. 2013. *Bacteroides reticulotermitis* sp. nov., isolated from the gut of a subterranean termite (*Reticulitermes speratus*). *International Journal of Systematic and Evolutionary Microbiology* 63 (Pt 2):691–5. doi: 10.1099/ijs.0.040931-0.

Sakamoto, M., N. Suzuki, and Y. Benno. 2010. *hsp60* and 16S rRNA gene sequence relationships among species of the genus *Bacteroides* with the finding that *Bacteroides suis* and *Bacteroides tectus* are heterotypic synonyms of *Bacteroides pyogenes*. *International Journal of Systematic and Evolutionary Microbiology* 60 (Pt 12):2984–-90. doi: 10.1099/ijs.0.021154-0.

Salyers, A. A., F. Gherardini, and M. O'Brien. 1981. Utilization of xylan by two species of human colonic *Bacteroides*. *Applied and Environmental Microbiology* 41 (4):1065–8. doi: 10.1128/AEM.41.4.1065-1068.1981.

Salyers, A. A., S. E. West, J. R. Vercellotti, and T. D. Wilkins. 1977. Fermentation of mucins and plant polysaccharides by anaerobic bacteria from the human colon. *Applied and Environmental Microbiology* 34 (5):529–33. doi: 10.1128/AEM.34.5.529-533.1977.

Sánchez, E., G. De Palma, A. Capilla, E. Nova, T. Pozo, G. Castillejo, V. Varea, A. Marcos, J. A. Garrote, I. Polanco, et al. 2011. Influence of environmental and genetic factors linked to celiac disease risk on infant gut colonization by *Bacteroides* species. *Applied and Environmental Microbiology* 77 (15):5316–23. doi: 10.1128/AEM.00365-11.

Sanfilippo, L., C. K. Li, R. Seth, T. J. Balwin, M. G. Menozzi, and Y. R. Mahida. 2010. *Bacteroides fragilis* enterotoxin induces the expression of IL-8 and transforming growth factor-beta (TGF-beta) by human colonic epithelial cells. *Clinical and Experimental Immunology* 119 (3):456–63. doi: 10.1046/j.1365-2249.2000.01155.x.

Saputra, S., Irisawa, T. M. Sakamoto, M. Kitahara, Sulistiani, T. Yulinery, M. Ohkuma, and A. Dinoto. 2015. *Bacteroides caecigallinarum* sp. nov. isolated from caecum of indonesian chicken. *International Journal of Systematic and Evolutionary Microbiology* 65 (12):4341–6. doi: 10.1099/ijsem.0.000573.

Sato, K., W. Kumita, T. Ode, S. Ichinose, A. Ando, Y. Fujiyama, T. Chida, and N. Okamura. 2010. ompA variants affecting the adherence of ulcerative colitis-derived *Bacteroides vulgatus*. *Journal of Medical and Dental Sciences* 57 (1):55–64.

Scholten-Koerselman, I., F. Houwaard, P. Janssen, and A. J. Zehnder. 1986. *Bacteroides xylanolyticus* sp. nov., a xylanolytic bacterium from methane producing cattle manure. *Antonie Van Leeuwenhoek* 52 (6):543–54. doi: 10.1007/BF00423415.

Sears, C. L. 2009. Enterotoxigenic *Bacteroides fragilis*: A rogue among symbiotes. *Clinical Microbiology Reviews* 22 (2):349–69. doi: 10.1128/CMR.00053-08.

Sellon, R. K., S. Tonkonogy, M. Schultz, L. A. Dieleman, W. Grenther, E. Balish, D. M. Rennick, and R. B. Sartor. 1998. Resident enteric bacteria are necessary for development of spontaneous colitis and immune system activation in Interleukin-10-deficient mice. *Infection and Immunity* 66 (11):5224–31. doi: 10.5840/newvico198862.

Shen, Y., M. L. Giardino Torchia, G. W. Lawson, C. L. Karp, J. D. Ashwell, and S. K. Mazmanian. 2012. Outer membrane vesicles of a human commensal mediate immune regulation and disease protection. *Cell Host & Microbe* 12 (4):509–20. doi: 10.1016/j.chom.2012.08.004.

Shin, Y., S.-J. Park, J. Paek, J.-S. Kim, M.-S. Rhee, H. Kim, J.-K. Kook, and Y.-H. Chang. 2017. *Bacteroides koreensis* sp. nov. and *Bacteroides kribbi* sp. nov., two new members of the genus Bacteroides. *International Journal of Systematic and Evolutionary Microbiology* 67 (11):4352–7. doi: 10.1099/ijsem.0.002226.

Shipman, J. A., J. E. Berleman, and A. A. Salyers. 2000. Characterization of Four outer membrane proteins involved in binding starch to the cell surface of *Bacteroides thetaiotaomicron*. *Journal of Bacteriology* 182 (19):5365–72. doi: 10.1128/JB.182.19.5365-5372.2000.

Skerman, V. B. D., V. Mcgowan, and P. H. A. Sneath. 1980a. Approved lists of bacterial names. *Medical Journal of Australia* 2 (1):3–4. doi: 10.5694/j.1326-5377.1980.tb131800.x.

Skerman, V. B. D., V. McGowan, and P. H. A. Sneath. 1980b. Approved lists of bacterial names. *International Journal of Systematic and Evolutionary Microbiology* 30 (1):225–420. doi: 10.1099/00207713-30-1-225.

Sommese, L., C. Pagliuca, B. Avallone, R. Ippolito, A. Casamassimi, V. Costa, R. Colicchio, R. Cerciello, M. D'Armiento, M. Scarpato, et al. 2012. Evidence of *Bacteroides fragilis* protection from *Bartonella henselae*-induced damage. *Plos One* 7 (11):e49653. doi: 10.1371/journal.pone.0049653.

Song, Y. L., C. X. Liu, M. Mcteague, and S. M. Finegold. 2004. "Bacteroides nordii" sp. nov. and "Bacteroides salyersae" sp. nov. isolated from clinical specimens of human intestinal origin . *Journal*

of Clinical Microbiology 42 (12):5565–70. doi: 10.1128/JCM.42.12.5565-5570.2004.

Sonnenburg, E. D., H. Zheng, P. Joglekar, S. K. Higginbottom, S. J. Firbank, D. N. Bolam, and J. L. Sonnenburg. 2010. Specificity of polysaccharide use in intestinal *Bacteroides* species determines diet-induced microbiota alterations. *Cell* 141 (7):1241–52. doi: 10.1016/j.cell.2010.05.005.

Stappenbeck, T. S., L. V. Hooper, and J. I. Gordon. 2002. Developmental regulation of intestinal angiogenesis by indigenous microbes via Paneth cells. *Proceedings of the National Academy of Sciences of the United States of America* 99 (24):15451–5. doi: 10.1073/pnas.202604299.

Stellwag, E. J., and P. B. Hylemon. 1976. Purification and characterization of bile salt hydrolase from *Bacteroides fragilis* subsp. *fragilis*. *Biochimica et Biophysica Acta* 452 (1):165–76. doi: 10.1016/0005-2744(76)90068-1.

Surana, N. K., and D. L. Kasper. 2012. The yin yang of bacterial polysaccharides: Lessons learned from *B. fragilis* PSA. *Immunological Reviews* 245 (1):13–26. doi: 10.1111/j.1600-065X.2011.01075.x.

Tajkarimi, M., and H. M. Wexler. 2017. CRISPR-Cas systems in *Bacteroides fragilis*, an important pathobiont in the human gut microbiome. *Frontiers in Microbiology* 8:2234. doi: 10.3389/fmicb.2017.02234.

Tan, H., J. Zhao, H. Zhang, Q. Zhai, and W. Chen. 2019. Novel strains of *Bacteroides fragilis* and *Bacteroides ovatus* alleviate the LPS-induced inflammation in mice. *Applied Microbiology and Biotechnology* 103 (5):2353–65. doi: 10.1007/s00253-019-09617-1.

Tasse, L., J. Bercovici, S. Pizzut-Serin, P. Robe, J. Tap, C. Klopp, B. L. Cantarel, P. M. Coutinho, B. Henrissat, M. Leclerc, et al. 2010. Functional metagenomics to mine the human gut microbiome for dietary fiber catabolic enzymes. *Genome Research* 20 (11):1605–12. doi: 10.1101/gr.108332.110.

Terrapon, N., V. Lombard, H. J. Gilbert, and B. Henrissat. 2015. Automatic prediction of polysaccharide utilization loci in *Bacteroidetes* species. *Bioinformatics (Oxford, England)* 31 (5):647–55. doi: 10.1093/bioinformatics/btu716.

Thiele Orberg, E., H. Fan, A. J. Tam, C. M. Dejea, C. E. Destefano Shields, S. Wu, L. Chung, B. B. Finard, X. Wu, P. Fathi, et al. 2017. The myeloid immune signature of enterotoxigenic *Bacteroides fragilis*-induced murine colon tumorigenesis. *Mucosal Immunology* 10 (2):421–33. doi: 10.1038/mi.2016.53.

Troy, E. B., and D. L. Kasper. 2010. Beneficial effects of *Bacteroides fragilis* polysaccharides on the immune system. *Frontiers in Bioscience (Landmark Edition)* 15 (1):25–34. doi: 10.2741/3603.

Ueki, A., K. Abe, N. Kaku, K. Watanabe, and K. Ueki. 2008. *Bacteroides propionicifaciens* sp. nov., isolated from rice-straw residue in a methanogenic reactor treating waste from cattle farms . *International Journal of Systematic and Evolutionary Microbiology* 58 (Pt 2):346–52. doi: 10.1099/ijs.0.65486-0.

Ueki, A., K. Abe, Y. Ohtaki, N. Kaku, K. Watanabe, and K. Ueki. 2011. *Bacteroides paurosaccharolyticus* sp. nov., isolated from a methanogenic reactor treating waste from cattle farms. *International Journal of Systematic and Evolutionary Microbiology* 61 (Pt 2):448–53. doi: 10.1099/ijs.0.022566-0.

Ulsemer, P., G. Henderson, K. Toutounian, A. Löffler, J. Schmidt, U. Karsten, M. Blaut, and S. Goletz. 2013. Specific humoral immune response to the Thomsen-Friedenreich tumor antigen (CD176) in mice after vaccination with the commensal bacterium *Bacteroides ovatus* D-6. *Cancer Immunology, Immunotherapy : CII* 62 (5):875–87. doi: 10.1007/s00262-013-1394-x.

Ulsemer, P., K. Toutounian, G. Kressel, C. Goletz, J. Schmidt, U. Karsten, A. Hahn, and S. Goletz. 2016. Impact of oral consumption of heat-treated *Bacteroides xylanisolvens* DSM 23964 on the level of natural TFα-specific antibodies in human adults. *Beneficial Microbes* 7 (4):485–500. doi: 10.3920/BM2015.0143.

Ulsemer, P., K. Toutounian, J. Schmidt, J. Leuschner, U. Karsten, and S. Goletz. 2012b. Safety assessment of the commensal strain *Bacteroides xylanisolvens* DSM 23964. *Regulatory Toxicology and Pharmacology : RTP* 62 (2):336–46. doi: 10.1016/j.yrtph.2011.10.014.

Ulsemer, P., K. Toutounian, J. Schmidt, U. Karsten, and S. Goletz. 2012c. Preliminary safety evaluation of a new *Bacteroides xylanisolvens* isolate. *Applied and Environmental Microbiology* 78 (2):528–35. doi: 10.1128/AEM.06641-11.

Ulsemer, P., Toutounian, K. G. Kressel, J. Schmidt, U. Karsten, U. A. Hahn, and S. Goletz. 2012a. Safety and tolerance of *Bacteroides xylanisolvens* DSM 23964 in healthy adults. *Beneficial Microbes* 3 (2):99–111. doi: 10.3920/BM2011.0051.

Valentine, P. J., and A. A. Salyers. 1992. Analysis of proteins associated with growth of *Bacteroides ovatus* on the branched galactomannan guar gum. *Applied and Environmental Microbiology* 58 (5):1534–40. doi: 10.1002/yea.320080602.

Veillon, A., and A. Zuber. 1898. Recherches sur quelques microbes strictement anaérobies et leur rôle en pathologie. *Archives de Mèdecine Expérimentale et d'Anatomie. Pathologique* 10:517–45.

Vich Vila, A., V. Collij, S. Sanna, T. Sinha, F. Imhann, A. R. Bourgonje, Z. Mujagic, D. M. A. E. Jonkers, A. A. M. Masclee, J. Fu, et al. 2020. Impact of commonly used drugs on the composition and metabolic function of the gut microbiota. *Nature Communications* 11 (1):362doi: 10.1038/s41467-019-14177-z.

Waidmann, M., O. Bechtold, J.-S. Frick, H.-A. Lehr, S. Schubert, U. Dobrindt, J. Loeffler, E. Bohn, and I. B. Autenrieth. 2003. *Bacteroides vulgatus* protects against *Escherichia coli*-induced colitis in gnotobiotic interleukin-2-deficient mice. *Gastroenterology* 125 (1):162–77. doi: 10.1016/S0016-5085(03)00672-3.

Wang, Y., H. Deng, Z. Li, Y. Tan, Y. Han, X. Wang, Z. Du, Y. Liu, R. Yang, Y. Bai, et al. 2017. Safety evaluation of a novel strain of *Bacteroides fragilis*. *Frontiers in Microbiology* 8:435. doi: 10.3389/fmicb.2017.00435.

Watanabe, Y., F. Nagai, M. Morotomi, H. Sakon, and R. Tanaka. 2010. *Bacteroides clarus* sp. nov., Bacteroides fluxus sp. nov. and Bacteroides oleiciplenus sp. nov., isolated from human faeces. *International Journal of Systematic and Evolutionary Microbiology* 60 (Pt 8):1864–9. doi: 10.1099/ijs.0.015107-0.

Weaver, J., T. R. Whitehead, M. A. Cotta, P. C. Valentine, and A. A. Salyers. 1992. Genetic analysis of a locus on the *Bacteroides ovatus* chromosome which contains xylan utilization genes. *Applied and Environmental Microbiology* 58 (9):2764–70. doi: 10.1016/0378-1097(92)90407-F.

Wei, B., H. Dalwadi, L. K. Gordon, C. Landers, D. Bruckner, S. R. Targan, and J. Braun. 2001. Molecular cloning of a *Bacteroides caccae* TonB-linked outer membrane protein identified by an inflammatory bowel disease marker antibody. *Infection and Immunity* 69 (10):6044–54. doi: 10.1128/IAI.69.10.6044-6054.2001.

Wensinck, F., C.-V. Lieshout, P. A. Poppelaars-Kustermans, and A. M. Schröder. 1981. The faecal flora of patients with Crohn's disease. *Journal of Hygiene* 87 (1):1–12. doi: 10.1017/s0022172400069187.

Werner, H. 1974. Differentiation and medical importance of saccharolytic intestinal *Bacteroides*. *Arzneimittel-Forschung* 24 (3):340–3.

Wexler, A. G., and A. L. Goodman. 2017. An insider's perspective: *Bacteroides* as a window into the microbiome. *Nature Microbiology* 2 (5):17026. doi: 10.1038/nmicrobiol.2017.26.

Whitehead, T. R., M. A. Cotta, M. D. Collins, E. Falsen, and P. A. Lawson. 2005. *Bacteroides coprosuis* sp. nov., isolated from swine-manure storage pits. *International Journal of Systematic and Evolutionary Microbiology* 55 (Pt 6):2515–8. doi: 10.1099/ijs.0.63869-0.

Wick, E. C., S. Rabizadeh, E. Albesiano, X. Wu, S. Wu, J. Chan, K.-J. Rhee, G. Ortega, D. L. Huso, D. Pardoll, et al. 2014. Stat3 activation in murine colitis induced by enterotoxigenic *Bacteroides fragilis*. *Inflammatory Bowel Diseases* 20 (5):821–34. doi: 10.1097/MIB.0000000000000019.

Wu, S., J. L. Powell, N. N. Mathioudakis, S. Kane, E. Fernandez, and C. L. Sears. 2004. *Bacteroides fragilis* enterotoxin induces intestinal epithelial cell secretion of interleukin-8 through mitogen-activated protein kinases and a tyrosine kinase-regulated nuclear factor-kappaB pathway. *Infection and Immunity* 72 (10):5832– 9. doi: 10.1128/IAI.72.10.5832-5839.2004.

Wu, S., P. J. Morin, D. Maouyo, and C. L. Sears. 2003. *Bacteroides fragilis* enterotoxin induces c-Myc expression and cellular proliferation. *Gastroenterology* 124 (2):392–400. doi: 10.1053/gast.2003.50047.

Xie, G., X. Wang, P. Liu, R. Wei, W. Chen, C. Rajani, B. Y. Hernandez, R. Alegado, B. Dong, D. Li, et al. 2016. Distinctly altered gut microbiota in the progression of liver disease. *Oncotarget* 7 (15): 19355–66. doi: 10.18632/oncotarget.8466.

Xu, J., and J. I. Gordon. 2003. Honor thy symbionts. *Proceedings of the National Academy of Sciences of the United States of America* 100 (18):10452–9. doi: 10.1073/pnas.1734063100.

Xu, J., M. K. Bjursell, J. Himrod, S. Deng, L. K. Carmichael, H. C. Chiang, L. V. Hooper, and J. I. Gordon. 2003. A genomic view of the human-*Bacteroides thetaiotaomicron* symbiosis. *Science (New York, N.Y.)* 299 (5615):2074–6. doi: 10.1126/science.1080029.

Yanagibashi, T., A. Hosono, A. Oyama, M. Tsuda, A. Suzuki, S. Hachimura, Y. Takahashi, Y. Momose, K. Itoh, K. Hirayama, et al. 2013. IgA production in the large intestine is modulated by a different mechanism than in the small intestine: *Bacteroides acidifaciens* promotes IgA production in the large intestine by inducing germinal center formation and increasing the number of IgA + B cells. *Immunobiology* 218 (4):645–51. doi: 10.1016/j.imbio.2012.07.033.

Yang, J.-Y., Y.-S. Lee, Y. Kim, S.-H. Lee, S. Ryu, S. Fukuda, K. Hase, C.-S. Yang, H. S. Lim, M.-S. Kim, et al. 2017. Gut commensal *Bacteroides acidifaciens* prevents obesity and improves insulin sensitivity in mice. *Mucosal Immunology* 10 (1):104–16. doi: 10.1038/mi.2016.42.

Yarza, P., C. Spröer, J. Swiderski, N. Mrotzek, S. Spring, B.-J. Tindall, S. Gronow, R. Pukall, H.-P. Klenk, E. Lang, et al. 2013. Sequencing orphan species initiative (sos): Filling the gaps in the 16s rRNA gene sequence database for all species with validly published names. *Systematic and Applied Microbiology* 36 (1):69–73. doi: 10.1016/j.syapm.2012.12.006.

Yu, S. Y., J.-S. Kim, B. S. Oh, S.-H. Park, S. W. Kang, J.-E. Park, S.-H. Choi, K.-I. Han, K. C. Lee, M. K. Eom, et al. 2019. *Bacteroides faecalis* sp. nov., isolated from human faeces. *International Journal of Systematic and Evolutionary Microbiology* 69 (12):3824–9. doi: 10.1099/ijsem.0.003690.

Zhang, W., B. Zhu, J. Xu, Y. Liu, E. Qiu, Z. Li, Z. Li, Y. He, H. Zhou, Y. Bai, et al. 2018. *Bacteroides fragilis* protects against antibiotic-associated diarrhea in rats by modulating intestinal defenses. *Frontiers in Immunology* 9:1040. doi: 10.3389/fimmu.2018.01040.

Zhuo, X.-G., M. K. Melby, and S. Watanabe. 2004. Soy isoflavone intake lowers serum LDL cholesterol: A meta-analysis of 8 randomized controlled trials in humans. *The Journal of Nutrition* 134 (9): 2395–400. doi: 10.1093/jn/134.9.2395.

Zimmermann, M., M. Zimmermann-Kogadeeva, R. Wegmann, and A. L. Goodman. 2019. Mapping human microbiome drug metabolism by gut bacteria and their genes. *Nature* 570 (7762):462–7. doi: 10.1038/s41586-019-1291-3.

Zitomersky, N. L., M. J. Coyne, and L. E. Comstock. 2011. Longitudinal analysis of the prevalence, maintenance, and IgA response to species of the order Bacteroidales in the human gut. *Infection and Immunity* 79 (5):2012–20. doi: 10.1128/iai.01348-10.

Zocco, M. A., M. E. Ainora, G. Gasbarrini, and A. Gasbarrini. 2007. *Bacteroides thetaiotaomicron* in the gut: Molecular aspects of their interaction. *Digestive and Liver Disease : Official Journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver* 39 (8):707–12. doi: 10.1016/j.dld.2007.04.003.