World Journal of Gastroenterology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.3748/wjg.v20.i47.17727

World J Gastroenterol 2014 December 21; 20(47): 17727-17736
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (17): Intestinal microbiota

Impact of the gut microbiota on rodent models of human disease

Axel Kornerup Hansen, Camilla Hartmann Friis Hansen, Lukasz Krych, Dennis Sandris Nielsen

Axel Kornerup Hansen, Camilla Hartmann Friis Hansen, Section of Experimental Animal Models, Department of Veterinary Disease Biology, University of Copenhagen, 1871 Frederiksberg, Denmark
Lukasz Krych, Dennis Sandris Nielsen, Department of Food Science, Faculty of Sciences, University of Copenhagen, 1958 Frederiksberg, Denmark
Author contributions: All authors contributed to this paper equally.
Correspondence to: Axel Kornerup Hansen, Professor, DVSc, DVM, DipECLAM, Section of Experimental Animal Models, Department of Veterinary Disease Biology, University of Copenhagen, 57 Thorvaldsensvej, 1871 Frederiksberg, Denmark. akh@sund.ku.dk
Telephone: +45-353-32726 Fax: +45-353-32755
Received: February 27, 2014 Revised: September 30, 2014
Accepted: November 18, 2014
Published online: December 21, 2014

Abstract

Traditionally bacteria have been considered as either pathogens, commensals or symbionts. The mammal gut harbors 10^{14} organisms dispersed on approximately 1000 different species. Today, diagnostics, in contrast to previous cultivation techniques, allow the identification of close to 100% of bacterial species. This has revealed that a range of animal models within different research areas, such as diabetes, obesity, cancer, allergy, behavior and colitis, are affected by their gut microbiota. Correlation studies may for some diseases show correlation between gut microbiota composition and disease parameters higher than 70%. Some disease phenotypes may be transferred when recolonizing germ free mice. The mechanistic aspects are not clear, but some examples on how gut bacteria stimulate receptors, metabolism, and immune responses are discussed. A more deeper understanding of the impact of microbiota has its origin in the overall composition of the microbiota and in some newly recognized species, such as *Akkermansia muciniphila*, Segmented filamentous bacteria and *Faecalibacterium prausnitzii*, which seem to have an impact on more or less severe disease in specific models. Thus, the impact of the microbiota on animal models is of a magnitude that cannot be ignored in future research. Therefore, either models with specific microbiota must be developed, or the microbiota must be characterized in individual studies and incorporated into data evaluation.

Key words: Animal models; Gut microbiota; Diabetes; Obesity; Cancer; Allergy; Behavior; Colitis

Core tip: Full characterization of the gut microbiota of animal models has revealed that animal models within different research areas, such as diabetes, obesity, cancer, allergy, behavior and colitis, are highly affected by their gut microbiota. The mechanistic aspects are not clear; however, the impact of the microbiota on animal models is of a magnitude that cannot be ignored in future research. Therefore, either models with specific microbiota must be developed, or the microbiota must be characterized in individual studies and incorporated into data evaluation.

Hansen AK, Friis Hansen CH, Krych L, Nielsen DS. Impact of the gut microbiota on rodent models of human disease. *World J Gastroenterol* 2014; 20(47): 17727-17736 Available from: URL: http://www.wjgnet.com/1007-9327/full/v20/i47/17727.htm DOI: http://dx.doi.org/10.3748/wjg.v20.i47.17727

INTRODUCTION

Host-microbiota relationship

The gut is an ideal incubation chamber for bacteria adapted to the mammal body temperature and the anaer-

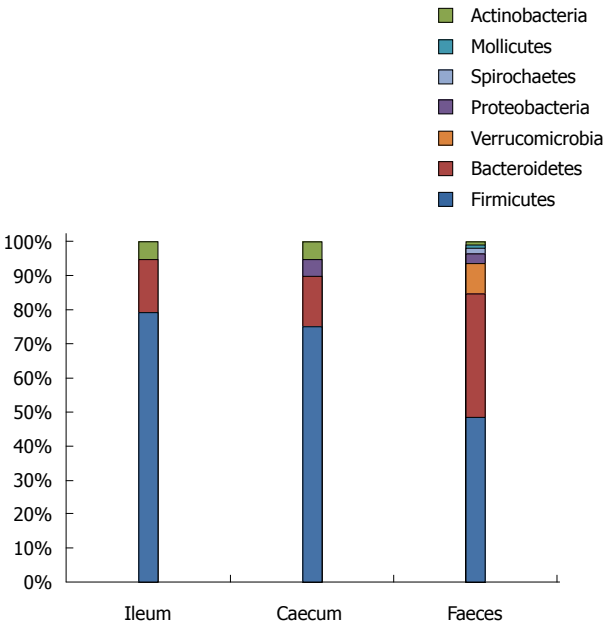

Figure 1 The approximate composition of the gut microbiota in the ileum, cecum and feces of mice[3,7,8,11,16].

obic environment. Thousands of years of co-existence has led to such adaptation, and the mammal gut harbors 10^{14} organisms dispersed over approximately 1000 different species, dependent on how the cut-offs are set for similarity. Within the traditional approach to laboratory animal bacteriology, bacteria have been considered as either pathogens, commensals or symbionts; however, there seems to be a need for a broader understanding of this. When first inside the gut, the bacteria will be fed and will be allowed to propagate, while the host organism will benefit from otherwise unavailable products of microbial digestion. Generally, pathogenicity is not in the interest of the microorganism, because it induces a strong and eradicating immune response from the host, and even in the case of microbial victory in this battle, the end result may be the death of the host and the need for the microbe to relocate to a new habitat. The host immune system, on the other hand, needs to protect the host from invasion without being so aggressive that it loses the microbe and thereby all its benefits.

Complexity of microbial impact on the host

A more advanced understanding of the impact of the microbiota takes into consideration both the overall composition and the balance between the members of the microbiota, as well as some newly recognized species, which, by themselves, seem to have an effect on the specific models. Some of these have a symbiotic effect, while others push disease development in a more detrimental direction. However, same species may act in favor of the development of one disease, while being more protective against another disease, and the mechanistic potential of the species may differ between different parts of the gut. For most of these bacteria, it is their abundance, rather than their qualitative presence or absence, which are responsible for their effect on the host[1-4]. The microbiota is normally not very diverse in the upper part of the gut, *e.g.* in the ileum, where there is a huge accumulation of lymphatic tissue available for stimulation[3,5-10]. It gradually becomes more diverse as the gut contents pass through the large intestine and become feces (Figure 1)[3,5-11]. In both man and mouse, a microbiota with a low diversity is indicative of an increased risk of developing inflammatory disease[12,13]. Furthermore, in animals, a microbiota that is roughly similar in the upper part of the gut, may differ substantially in the lower part of the gut and *vice versa*[3,14]. Finally, there might be essential differences between the effects of the various species at different ages of the animals, which may explain why some species favor the development of one disease, while protecting against another.

Modern microbiological identification techniques

Over recent decades, new methods based upon molecular biology diagnostics have been developed. Such methods, which include quantitative real-time polymerase chain reaction (qPCR) assays[15], pyrosequencing[16] and metagenomic sequencing, have permitted identification of close to 100% of the gut's operational taxonomic units (OTU), which include both cultivable and non-cultivable bacterial species, and in principle, viral, eukaryotes and Archea[17], although they are seldom specifically tested for at present. In contrast, previous cultivation techniques only allowed cultivation and identification of 10%-20% of the bacterial species present in the gut[18]. These molecular biology-based tools have enabled detailed correlation studies. Such studies have revealed that a range of animal models within a range of different research areas are affected by their gut microbiota[19].

GENERAL MECHANISMS UNDERLYING THE GUT MICROBIOTA EFFECT

As described below, the impact of the microbiota on animal models is well documented, while the mechanisms underlying this are less clear. Some hypotheses, though, make more sense than others. As techniques for the full characterization of the microbiota have been developed over the last decade, we are only now beginning to achieve an understanding of how the microbiota actually exerts its effect on the host; however, some examples can be given.

Window of opportunity

In early life, there is a window for the induction of oral tolerance in the gut[20]. This seems essential to avoid inflammatory disease later in life[21]. Molecular structures in bacteria known as microbial-associated molecular patterns (MAMP) stimulate pattern-recognition receptors (PRR) in the host, thereby inducing innate responses[22]. Among the most important PRRs are the toll-like receptors (TLR), which are present in different types on a range of different cell types[22-29] (Figure 2). An impor-

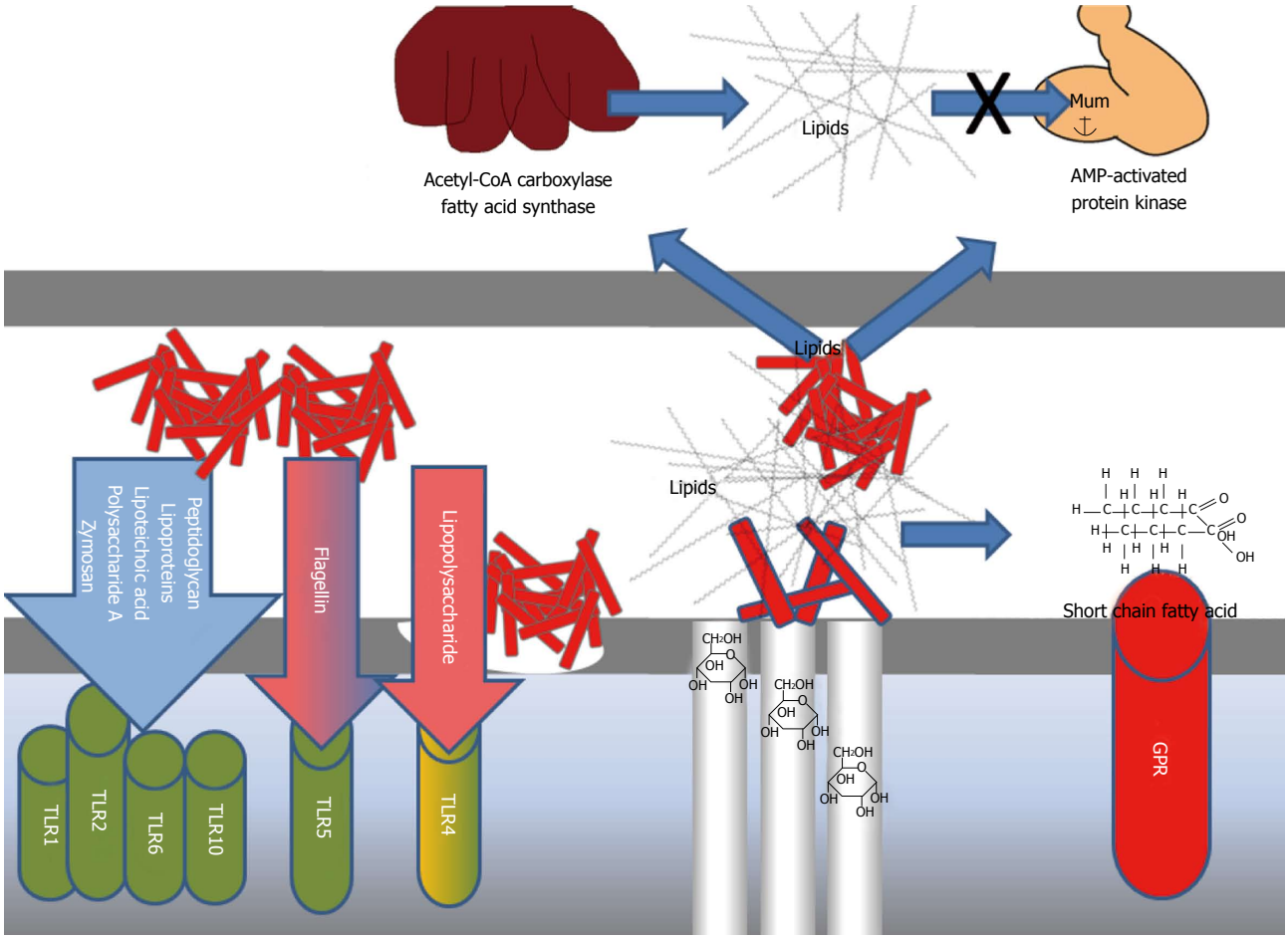

Figure 2 Examples of some theories on potential pathways for the impact of gut microbiota on animal models of human disease. Bacterial colonization may double the density of capillaries in the small intestinal epithelium, thereby promoting intestinal monosaccharide absorption[28]. Undigested food components may be fermented into SCFAs and subsequently act as signals for GPRs of importance for the development of obesity[26,29]. Bacteria may express several key enzymes relevant for hepatic lipogenesis[27,50], and hepatic and muscular fatty acid oxidation[31]. Molecular structures in the cell walls of bacteria may act as MAMPs, which stimulate TLRs on the host cells to induce innate immune responses. The complex of TLR1, TLR2, TLR6 and TLR10 is expressed on a range of cell types such as enterocytes, macrophages, dendritic cells, natural killer cells, mast cells, T cells, B cells, neutrophilic cells and Schwann cells, and may be stimulated by various MAMPs, *e.g.* peptidoglycan, from Gram positive bacteria cell types[21,23-25,31-33]. TLR4, expressed by *e.g.* macrophages, dendritic cells, mast cells, natural killer cells and enterocytes, is stimulated by lipopolysaccharides from Gram negative bacteria[30], while flagellin from various bacteria may stimulate TLR5 expressed by *e.g.* mucosal dendritic cells and macrophages[33]. Mucin-degrading *Akkermansia muciniphila* may reduce the mucus layer to increase TLR-stimulation[79]. SCFAs: Short chain fatty acids; GPR: G-protein receptor; MAMP: Microbial-associated molecular pattern; TLR: Toll-like receptor.

tant example of a MAMP is lipopolysaccharides (LPS), which are important parts of the cell wall of Gram negative bacteria[30], such as Proteobacteria[31], from which it stimulates TLR4. Another important example is peptidoglycan, found in the cell walls of Gram positive bacteria, which stimulates TLR2[32] and flagellin deriving from flagellated bacteria, leading to stimulation of TLR5[33]. Therefore, as different types of MAMPs stimulate different TLR's dispersed on a variety of different cell types[23], and as MAMPs are also dispersed and shared between members of the microbiota[22], there is a vast range of innate host responses to bacteria.

Adult life stimulation

The age of the animal also makes a difference. For example, stimulation of TLR1, TLR2 and TLR4 in early life leads to higher production of interleukin (IL)-6 than stimulation later in life[34]. Germ free animals have more T helper cells type 2 (TH2) and less TH1 cells[35], as the stimulation of the gut lamina propria dendritic cells, *e.g.* by polysaccharide A (PSA) from *Bacteroides fragilis,* induces IL-12 secretion, which favors TH1 at the cost of TH2[36]. Host-bacterial interactions, probably mediated through glucagon-like peptide 2 (GLP-2), seem to control the gut barrier function[37]. Metabolic endotoxaemia is responsible for the phenomenon whereby excess intake of dietary fat increases plasma LPS levels[38,39], which in mice, is a sufficient molecular mechanism to trigger metabolic diseases, such as obesity and diabetes[40].

EXAMPLES OF SOME ANIMAL MODELS UNDER IMPACT OF THE GUT MICROBIOTA

Impact of germ free status

The clearest documentation of a general microbial impact on rodent models is observed when comparing a conven-

Table 1 Examples of rodent models in which germ free status has a documented impact

Model	Disease
Models with increased disease incidence or severity	
β-lactoglobulin induced mouse[51]	Allergy
NOD mouse[42]	Type 1 diabetes
MyD88 KO NOD mouse[42]	Type 1 diabetes
Restrained mouse[43]	Stress
Models with decreased disease incidence or severity	
Ovalbumin-specific TCR TG mouse[44]	Allergy
Swiss-Webster mouse[45]	Anxiety
Collagen induced rat[52]	Arthritis
HLA-B27 TG rat[53]	IBD
IL-2 KO mouse[54,55]	IBD
IL-10 KO mouse[56]	IBD
TCRα KO mouse[57]	IBD
Dextran sulfate sodium induced mouse[46]	IBD
SAMP1/Yit mouse[47]	IBD
Adoptive T-cell transfer in the mouse[48]	IBD
Carrageenan, LPS, or formalin induced mouse[49]	Inflammatory pain
C57BL/6 mouse[65]	Obesity
C57BL/6 mouse[65]	Type 2 diabetes

NOD: Non-obese diabetic; MyD88: Myeloid differentiation primary response gene 88; KO: Knockout; TCR: T cell receptor; TG: Transgenic; HLA-B27: Human leucocyte antigen subtype B27; IL-2: Interleukin 2; SAMP1/Yit: Senescence accelerated mice prone line 1 Yakult; LPS: Lipopolysaccharide. IBD: Inflammatory bowel disease.

tional model with a microbiota with a germ free version. In several studies, this has revealed essential differences in disease expression (Table 1)[22,41-57]. Although germ free mice eat more, they are leaner, and they have less body fat compared with conventional mice because they are less efficient in extracting energy from their diet[50]. Germ free mice have increased expression of obesity-related peptides, such as glucagon-like peptide 1 (GLP-1) in the brain[58], which is relevant, because central GLP-1 reduces food intake in rats[59]. Germ free mice also behave differently from microbiota-harboring mice and this behavior may be normalized by colonization[43]. However, for this phenotype there also seems to be an important time window in early life[60]. Germ free mice with a mutation causing a defect in the skin barrier suffer from a more severe B-lymphoproliferative disorder, because they express significantly higher levels of the proinflammatory cytokine thymic stromal lymphopoietin[61]. Inflammatory bowel disease (IBD) occurs either because of a TH1/TH17 response (Crohn's disease) or a TH2 response (ulcerative colitis) to gut commensals[62]. Therefore, IBD under germ free conditions does not develop at all in, *e.g.* Human Leucocyte Antigen subtypes B27 (HLA-B27) transgenic rats[53] and IL-10 knockout mice[56]. For the IL-10 knockout mice[63] it does not occur even under barrier protected conditions (Table 1). IL-2 knockout mice may, under germ free conditions, show mild focal intestinal inflammation[64] (Table 1).

Impact of fluctuations in the gut microbiota composition

Within animal models of the metabolic syndrome, there seems to be an association between the gut microbiota and at least some of the metabolic parameters. For example, in leptin-deficient obese mice, there is a strong correlation between glycated hemoglobin levels and the composition of the gut microbiota[1]. Further, these mice have significantly more Firmicutes and fewer Bacteriodetes members compared with their wild-type and heterozygous litter mates[10]. Their obese phenotype may be transferred with the microbiota by recolonizing germ free lean wild-type mice[65]. In C57 Black substrain 6 (C57BL/6) mice on both high and low calorie diet, continuous oral ampicillin improves glucose tolerance[66,67]. However, this effect is mainly caused by an early life impact on glucose tolerance, and the effect ceases immediately after termination of treatment; thereafter, the glucose tolerance may even decrease[68,69]. Several studies describe cross-talk between the brain and the gut through both the vagal system and the hypothalamus-pituitary-adrenal (HPA) axis[70]. Stressing animal models changes their microbiota[71], and the composition of the gut microbiota has an impact on responses in rodent stress tests[72,73]. Innate immune system cytokines, such as IL-1, IL-6 and tumor necrosis factor α (TNFα), which may originate from a gut microbiota provocation, induce "sickness behavior", changing the priorities of the organism to enhance recovery and survival[74]. However, metabolites formed by microbial decomposition in the gut may also have a direct impact on the brain[75]. In mouse models of atopic dermatitis, more than 70% of the variation observed in the local tissue cytokine response may be shared with the variation in gut microbiota[76]. Changes in the structure of the microbial community seem to reduce the number, as well as the size, of tumors in azoxymethane/dextran sodium sulfate (AOM/DSS) colon cancer-induced mice, and tumor induction may be achieved by colonizing germ free mice with microbiota from induced mice[77].

EXAMPLES OF THE IMPACTS OF SPECIFIC BACTERIAL SPECIES

Verrucomicrobioa

Akkermansia muciniphila (*A. muciniphila*) is a Gram negative bacterium, which in mice is the only species belonging to the phylum Verrucomicrobia[78]. It interacts *via* its mucin degrading capabilities with enteroendocrine cells to modulate gut barrier function, and it is capable of producing certain short chain fatty acids (SCFA's) with a direct action on the receptor G-protein receptor 43 (GPR43)[79]. Abundance of *A. muciniphila* is reduced in mice with obesity and type 2 diabetes[80], and it gradually disappears as aging leptin deficient obese mice develop insulin resistance[1]. In non-obese diabetic (NOD) mice it becomes more abundant when mice are fed a gluten-free diet, which decreases the incidence of type 1 diabetes[81]. Early life treatment with vancomycin in NOD mice allows *A. muciniphila* to become a dominant gut microbiota member, which reduces the incidence of type 1 diabetes[3], but enhances susceptibility to allergic asthma[82], which

is in accordance with other studies showing allergy and diabetes to counteract one another in NOD mice[83,84]. Induction of IBD in mice with dextran sodium sulfate (DSS) reduces the number of extracellular vesicles derived from *A. muciniphila*, and feeding DSS induced mice such vesicles reduces the severity of IBD[85], which fits well with observations in humans[4]. However, it not only reduces the severity of diseases: its presence is correlated with higher severity when infecting mice with *Salmonella typhimurium*[86], and AOM/DSS colon cancer-induced mice have an increased abundance of *A. muciniphila*[77], which may be explained by its ability to downregulate the natural killer cell receptor, NKG2D, which is part of the anti-carcinogenic defense[87].

Firmicutes

Segmented filamentous bacteria (SFB's) are clostridia-related Gram-positive bacteria[88]. The term has been applied for decades to describe intestinal bacteria of a uniform morphology[89]. However, today the term refers to one single species, also known as *Candidatus Savagella*[90]. SFBs induce secretion of the pro-inflammatory cytokine IL-17 from TH17 cells[91], which in the adult mouse is correlated with a low number of regulatory T cells[92]. The presence of SFB's differs between mice from different vendors[92], and SFB positive NOD mice have a significantly lower incidence of type 1 diabetes compared with SFB negative ones[93]. In the adoptive transfer severe combined immune deficiency (SCID) mouse model of IBD, SFBs are essential for the induction of severe inflammation[48]. Furthermore, SFBs and the induced TH17 are important in the defense against intestinal pathogens. For example, mice infected with *Citrobacter rodentium*, a potent murine colon pathogen, exhibit severe symptoms if they lack SFBs[91].

IBD in IL-10 knockout mice is enhanced by *Enterococcus fecalis*[94,95], which is probably linked to its production of gelatinase[96].

Faecalibacterium prausnitzii (*F. prausnitzii*) is a clostridia-related bacterium[97] linked to a protective effect against human Crohn's disease[98]. Oral feeding of *F. prausnitzii* reduced the severity of 2,4,6-trinitrobenzenesulfonic acid (TNBS)-induced colitis in mice, and some studies indicated that this may also be the case in both multidrug resistance gene deficient (*mdr1a* knockout)[99] and in the DSS-induced mouse models of colitis[100].

High abundances of *Lactobacillus* spp. and bifidobacteria are correlated strongly with low levels of inflammation in mice[101] and leptin in rats[102], which also fits well with these bacteria acting protectively against IBD in IL-10 knockout mice[103], allergic sensitization in mice[104], and myocardial infarction in rats[102]. *Lachnospiraceae* seems quantitatively correlated to improved glucose tolerance in leptin-deficient obese mice[1].

In stressed mice, there is correlation between their Firmicutes levels and their responses in the stress tests[73]. Ingestion of *Lactobacillus rhamnosus* in mice regulates their emotional behavior and central γ-aminobutyric acid (GABA) receptor expression *via* the vagus nerve[72].

Bacteroidetes

A high abundance of the Gram negative family Prevotellaceae, perhaps restricted to one unclassified genus, in the gut of leptin-deficient obese mice correlated with impaired glucose tolerance[1].By contrast, in AOM/DSS induced colon cancer mice, a high abundance of Prevotellaceae correlated with a low tumor burden[77]. *P. copri*, which has been correlated with the development of arthritis in humans, seems to increase the severity of DSS induced colitis in mice[5]. *Caspase-3* knockout mice exhibit a lower inflammatory response to DSS induction of colitis compared with wild-type mice; however, this protective effect of the mutation is decreased by cohousing knockout mice with wild-type mice, which significantly increases the abundance of *Prevotella* spp. in the knockout mice[105].

Bacteroides vulgatus seems to enhance IBD in HLA-B27 transgenic rats[106] and IL-10 knockout mice[95], and in the Bio Breeding (BB) rat, a spontaneous type 1 diabetes model. The fecal microbiota differ and contain an increased number of *Bacteroides* spp. before onset of diabetes[107]. As in all other mammals, *Bacteroides* spp. form an important part of the Bacteroidetes fraction of the rodent gut[16]. These Gram negative bacteria are important for the processing of complex molecules to simpler ones in the gut[108]: complex glycans are their key source of energy[109]. *B. fragilis* toxins cause symptoms of diarrhea and IBD in germ-free mice[110], and they induce colonic tumors strongly in multiple intestinal neoplasia (MIN) mice[111]. On the other hand, *B. fragilis* PSA, which is important for the inflammatory gut response to pathogens[36], also protects against *Helicobacter hepaticus*-induced colitis in mice; probably *via* the prevention of IL-17 secretion[112]. Feeding the maternal immune activation (MIA) mouse model with *B. fragilis* reduces symptoms of autism, which is probably linked to the normalization of the levels of a specific gut metabolite[113].

The abundance of *Alistipes* spp., a bacterium of the Rikenellaceae family, seems to increase when mice are stressed by grid floor housing[73].

Proteobacteria

Escherichia coli (*E. coli*) enhances IBD in HLA-B27 overexpressing rats[106], although *E. coli* Nissle stabilizes the enteric barrier in mice[114]. When reducing type 1 diabetes by pre-weaning treatment of NOD mice with vancomycin, a vast increase in the abundance of Proteobacteria in the pups was observed[3].

Actinobacteria

Bifidobacterium spp. in rodents have a positive impact on the regulatory and innate immunity[101,115]. Perinatal supplementation of *B. longum* reduced TH1 and TH2 responses in allergen sensitized mice[104]. On the other hand, their numbers are also increased in gluten-fed NOD mice with a high incidence of type 1 diabetes compared with NOD

mice on a gluten-free diet[81].

DISCUSSION

The information gained over the last decade on how the entire microbiota, as well as some of its individual members, affect animal models of very different types, has prompted the scientific community to incorporate this in future production and quality assurance of animal models. It is not possible to regard these matters from a "Specific pathogen-free" concept, as some of the species act in favor of the development of one disease, while against the development of another disease, *e.g.* SFB's both protect against type 1 diabetes and induces a T_H17 response in favor of the development of Crohn's disease. Furthermore, the balance between the different fractions of the microbiota is also likely to make a difference. Ultimately, it is often a quantitative rather than a qualitative presence that makes the difference. Therefore, it is likely that we will see more tailor-made rodent models, *i.e.* commercial breeders and research groups have sought to produce animals with a specific microbiota for the conditions under test. One obvious idea may be to breed such animals by selective breeding; however, this does not seem to increase the microbiota similarity, although the microbiota of offspring show a clear clustering with the mother's microbiota[116,117]. It is probably rational to inoculate germ free mice with a tailor-made microbiota around weaning, as they are conventionalized in SPF conditions[118]. The window for induction of oral tolerance in animal models may also be turned around, such that a low bacterial stimulation in the open phase of this window may be essential to develop target diseases in the model. When stimulated later on, the nature of this stimulation is also essential, because commonly used disease models in rodents are driven by specific subsets of T cells[19]. Another alternative will be to characterize the microbiota composition for animals in sensitive studies and incorporate this in the data evaluation by chemometric or multifactorial statistical means. The impact of the gut microbiota on animal models is of a magnitude that cannot be neglected in the future.

REFERENCES

1 **Ellekilde M**, Krych L, Hansen CH, Hufeldt MR, Dahl K, Hansen LH, Sørensen SJ, Vogensen FK, Nielsen DS, Hansen AK. Characterization of the gut microbiota in leptin deficient obese mice - Correlation to inflammatory and diabetic parameters. *Res Vet Sci* 2014; **96**: 241-250 [PMID: 24556473 DOI: 10.1016/j.rvsc.2014.01.007]

2 **Brown CT**, Davis-Richardson AG, Giongo A, Gano KA, Crabb DB, Mukherjee N, Casella G, Drew JC, Ilonen J, Knip M, Hyöty H, Veijola R, Simell T, Simell O, Neu J, Wasserfall CH, Schatz D, Atkinson MA, Triplett EW. Gut microbiome metagenomics analysis suggests a functional model for the development of autoimmunity for type 1 diabetes. *PLoS One* 2011; **6**: e25792 [PMID: 22043294 DOI: 10.1371/journal.pone.0025792]

3 **Hansen CH**, Krych L, Nielsen DS, Vogensen FK, Hansen LH, Sørensen SJ, Buschard K, Hansen AK. Early life treatment with vancomycin propagates Akkermansia muciniphila and reduces diabetes incidence in the NOD mouse. *Diabetologia* 2012; **55**: 2285-2294 [PMID: 22572803 DOI: 10.1007/s00125-012-2564-7]

4 **Png CW**, Lindén SK, Gilshenan KS, Zoetendal EG, McSweeney CS, Sly LI, McGuckin MA, Florin TH. Mucolytic bacteria with increased prevalence in IBD mucosa augment in vitro utilization of mucin by other bacteria. *Am J Gastroenterol* 2010; **105**: 2420-2428 [PMID: 20648002 DOI: 10.1038/ajg.2010.281]

5 **Scher JU**, Sczesnak A, Longman RS, Segata N, Ubeda C, Bielski C, Rostron T, Cerundolo V, Pamer EG, Abramson SB, Huttenhower C, Littman DR. Expansion of intestinal Prevotella copri correlates with enhanced susceptibility to arthritis. *Elife* 2013; **2**: e01202 [PMID: 24192039 DOI: 10.7554/eLife.01202]

6 **Ubeda C**, Taur Y, Jenq RR, Equinda MJ, Son T, Samstein M, Viale A, Socci ND, van den Brink MR, Kamboj M, Pamer EG. Vancomycin-resistant Enterococcus domination of intestinal microbiota is enabled by antibiotic treatment in mice and precedes bloodstream invasion in humans. *J Clin Invest* 2010; **120**: 4332-4341 [PMID: 21099116 DOI: 10.1172/jci43918]

7 **Hildebrandt MA**, Hoffmann C, Sherrill-Mix SA, Keilbaugh SA, Hamady M, Chen YY, Knight R, Ahima RS, Bushman F, Wu GD. High-fat diet determines the composition of the murine gut microbiome independently of obesity. *Gastroenterology* 2009; **137**: 1716-1724.e1-e2 [PMID: 19706296 DOI: 10.1053/j.gastro.2009.08.042]

8 **Antonopoulos DA**, Huse SM, Morrison HG, Schmidt TM, Sogin ML, Young VB. Reproducible community dynamics of the gastrointestinal microbiota following antibiotic perturbation. *Infect Immun* 2009; **77**: 2367-2375 [PMID: 19307217 DOI: 10.1128/IAI.01520-08]

9 **Wilson KH**, Brown RS, Andersen GL, Tsang J, Sartor B. Comparison of fecal biota from specific pathogen free and feral mice. *Anaerobe* 2006; **12**: 249-253 [PMID: 17070078 DOI: 10.1016/j.anaerobe.2006.09.002]

10 **Ley RE**, Bäckhed F, Turnbaugh P, Lozupone CA, Knight RD, Gordon JI. Obesity alters gut microbial ecology. *Proc Natl Acad Sci USA* 2005; **102**: 11070-11075 [PMID: 16033867 DOI: 10.1073/pnas.0504978102]

11 **Walk ST**, Blum AM, Ewing SA, Weinstock JV, Young VB. Alteration of the murine gut microbiota during infection with the parasitic helminth Heligmosomoides polygyrus. *Inflamm Bowel Dis* 2010; **16**: 1841-1849 [PMID: 20848461 DOI: 10.1002/ibd.21299]

12 **Hildebrand F**, Nguyen TL, Brinkman B, Yunta RG, Cauwe B, Vandenabeele P, Liston A, Raes J. Inflammation-associated enterotypes, host genotype, cage and inter-individual effects drive gut microbiota variation in common laboratory mice. *Genome Biol* 2013; **14**: R4 [PMID: 23347395 DOI: 10.1186/gb-2013-14-1-r4]

13 **Qin J**, Li Y, Cai Z, Li S, Zhu J, Zhang F, Liang S, Zhang W, Guan Y, Shen D, Peng Y, Zhang D, Jie Z, Wu W, Qin Y, Xue W, Li J, Han L, Lu D, Wu P, Dai Y, Sun X, Li Z, Tang A, Zhong S, Li X, Chen W, Xu R, Wang M, Feng Q, Gong M, Yu J, Zhang Y, Zhang M, Hansen T, Sanchez G, Raes J, Falony G, Okuda S, Almeida M, LeChatelier E, Renault P, Pons N, Batto JM, Zhang Z, Chen H, Yang R, Zheng W, Li S, Yang H, Wang J, Ehrlich SD, Nielsen R, Pedersen O, Kristiansen K, Wang J. A metagenome-wide association study of gut microbiota in type 2 diabetes. *Nature* 2012; **490**: 55-60 [PMID: 23023125 DOI: 10.1038/nature11450]

14 **Pang W**, Vogensen FK, Nielsen DS, Hansen AK. Faecal and caecal microbiota profiles of mice do not cluster in the same way. *Lab Anim* 2012; **46**: 231-236 [PMID: 22723645 DOI: 10.1258/la.2012.011128]

15 **Bergström A**, Licht TR, Wilcks A, Andersen JB, Schmidt LR, Grønlund HA, Vigsnaes LK, Michaelsen KF, Bahl MI. Introducing GUt low-density array (GULDA): a validated approach for qPCR-based intestinal microbial community analysis. *FEMS Microbiol Lett* 2012; **337**: 38-47 [PMID: 22967145

DOI: 10.1111/1574-6968.12004]
16 **Krych L**, Hansen CH, Hansen AK, van den Berg FW, Nielsen DS. Quantitatively different, yet qualitatively alike: a meta-analysis of the mouse core gut microbiome with a view towards the human gut microbiome. *PLoS One* 2013; **8**: e62578 [PMID: 23658749 DOI: 10.1371/journal.pone.0062578]
17 **Qin J**, Li R, Raes J, Arumugam M, Burgdorf KS, Manichanh C, Nielsen T, Pons N, Levenez F, Yamada T, Mende DR, Li J, Xu J, Li S, Li D, Cao J, Wang B, Liang H, Zheng H, Xie Y, Tap J, Lepage P, Bertalan M, Batto JM, Hansen T, Le Paslier D, Linneberg A, Nielsen HB, Pelletier E, Renault P, Sicheritz-Ponten T, Turner K, Zhu H, Yu C, Li S, Jian M, Zhou Y, Li Y, Zhang X, Li S, Qin N, Yang H, Wang J, Brunak S, Doré J, Guarner F, Kristiansen K, Pedersen O, Parkhill J, Weissenbach J, Bork P, Ehrlich SD, Wang J. A human gut microbial gene catalogue established by metagenomic sequencing. *Nature* 2010; **464**: 59-65 [PMID: 20203603 DOI: 10.1038/nature08821]
18 **Zoetendal EG**, Collier CT, Koike S, Mackie RI, Gaskins HR. Molecular ecological analysis of the gastrointestinal microbiota: a review. *J Nutr* 2004; **134**: 465-472 [PMID: 14747690]
19 **Bleich A**, Hansen AK. Time to include the gut microbiota in the hygienic standardisation of laboratory rodents. *Comp Immunol Microbiol Infect Dis* 2012; **35**: 81-92 [PMID: 22257867 DOI: 10.1016/j.cimid.2011.12.006]
20 **Hansen CH**, Nielsen DS, Kverka M, Zakostelska Z, Klimesova K, Hudcovic T, Tlaskalova-Hogenova H, Hansen AK. Patterns of early gut colonization shape future immune responses of the host. *PLoS One* 2012; **7**: e34043 [PMID: 22479515 DOI: 10.1371/journal.pone.0034043]
21 **Weng M**, Walker WA. The role of gut microbiota in programming the immune phenotype. *J Dev Orig Health Dis* 2013; **4**: 203-214 [PMID: 24353893 DOI: 10.1017/S2040174412000712]
22 **Tlaskalová-Hogenová H**, Stepánková R, Hudcovic T, Tucková L, Cukrowska B, Lodinová-Zádníková R, Kozáková H, Rossmann P, Bártová J, Sokol D, Funda DP, Borovská D, Reháková Z, Sinkora J, Hofman J, Drastich P, Kokesová A. Commensal bacteria (normal microflora), mucosal immunity and chronic inflammatory and autoimmune diseases. *Immunol Lett* 2004; **93**: 97-108 [PMID: 15158604 DOI: 10.1016/j.imlet.2004.02.005]
23 **Kamdar K**, Nguyen V, DePaolo RW. Toll-like receptor signaling and regulation of intestinal immunity. *Virulence* 2013; **4**: 207-212 [PMID: 23334153 DOI: 10.4161/viru.23354]
24 **Souza-Fonseca-Guimaraes F**, Parlato M, Philippart F, Misset B, Cavaillon JM, Adib-Conquy M. Toll-like receptors expression and interferon-γ production by NK cells in human sepsis. *Crit Care* 2012; **16**: R206 [PMID: 23098236 DOI: 10.1186/cc11838]
25 **Sasai M**, Yamamoto M. Pathogen recognition receptors: ligands and signaling pathways by Toll-like receptors. *Int Rev Immunol* 2013; **32**: 116-133 [PMID: 23570313 DOI: 10.3109/08830185.2013.774391]
26 **Samuel BS**, Shaito A, Motoike T, Rey FE, Backhed F, Manchester JK, Hammer RE, Williams SC, Crowley J, Yanagisawa M, Gordon JI. Effects of the gut microbiota on host adiposity are modulated by the short-chain fatty-acid binding G protein-coupled receptor, Gpr41. *Proc Natl Acad Sci USA* 2008; **105**: 16767-16772 [PMID: 18931303 DOI: 10.1073/pnas.0808567105]
27 **Denechaud PD**, Dentin R, Girard J, Postic C. Role of ChREBP in hepatic steatosis and insulin resistance. *FEBS Lett* 2008; **582**: 68-73 [PMID: 17716660 DOI: 10.1016/j.febslet.2007.07.084]
28 **Stappenbeck TS**, Hooper LV, Gordon JI. Developmental regulation of intestinal angiogenesis by indigenous microbes via Paneth cells. *Proc Natl Acad Sci USA* 2002; **99**: 15451-15455 [PMID: 12432102 DOI: 10.1073/pnas.202604299]
29 **Bjursell M**, Admyre T, Göransson M, Marley AE, Smith DM, Oscarsson J, Bohlooly-Y M. Improved glucose control and reduced body fat mass in free fatty acid receptor 2-deficient mice fed a high-fat diet. *Am J Physiol Endocrinol Metab* 2011; **300**: E211-E220 [PMID: 20959533 DOI: 10.1152/ajpendo.00229.2010]
30 **Raetz CR**, Whitfield C. Lipopolysaccharide endotoxins. *Annu Rev Biochem* 2002; **71**: 635-700 [PMID: 12045108 DOI: 10.1146/annurev.biochem.71.110601.135414]
31 **Huber M**, Kalis C, Keck S, Jiang Z, Georgel P, Du X, Shamel L, Sovath S, Mudd S, Beutler B, Galanos C, Freudenberg MA. R-form LPS, the master key to the activation ofTLR4/MD-2-positive cells. *Eur J Immunol* 2006; **36**: 701-711 [PMID: 16506285 DOI: 10.1002/eji.200535593]
32 **Ozinsky A**, Underhill DM, Fontenot JD, Hajjar AM, Smith KD, Wilson CB, Schroeder L, Aderem A. The repertoire for pattern recognition of pathogens by the innate immune system is defined by cooperation between toll-like receptors. *Proc Natl Acad Sci USA* 2000; **97**: 13766-13771 [PMID: 11095740 DOI: 10.1073/pnas.250476497]
33 **Feuillet V**, Medjane S, Mondor I, Demaria O, Pagni PP, Galán JE, Flavell RA, Alexopoulou L. Involvement of Toll-like receptor 5 in the recognition of flagellated bacteria. *Proc Natl Acad Sci USA* 2006; **103**: 12487-12492 [PMID: 16891416 DOI: 10.1073/pnas.0605200103]
34 **Liao SL**, Yeh KW, Lai SH, Lee WI, Huang JL. Maturation of Toll-like receptor 1-4 responsiveness during early life. *Early Hum Dev* 2013; **89**: 473-478 [PMID: 23591080 DOI: 10.1016/j.earlhumdev.2013.03.013]
35 **Mazmanian SK**, Kasper DL. The love-hate relationship between bacterial polysaccharides and the host immune system. *Nat Rev Immunol* 2006; **6**: 849-858 [PMID: 17024229 DOI: 10.1038/nri1956]
36 **Mazmanian SK**, Liu CH, Tzianabos AO, Kasper DL. An immunomodulatory molecule of symbiotic bacteria directs maturation of the host immune system. *Cell* 2005; **122**: 107-118 [PMID: 16009137 DOI: 10.1016/j.cell.2005.05.007]
37 **Cani PD**, Possemiers S, Van de Wiele T, Guiot Y, Everard A, Rottier O, Geurts L, Naslain D, Neyrinck A, Lambert DM, Muccioli GG, Delzenne NM. Changes in gut microbiota control inflammation in obese mice through a mechanism involving GLP-2-driven improvement of gut permeability. *Gut* 2009; **58**: 1091-1103 [PMID: 19240062 DOI: 10.1136/gut.2008.165886]
38 **Cani PD**, Delzenne NM. Gut microflora as a target for energy and metabolic homeostasis. *Curr Opin Clin Nutr Metab Care* 2007; **10**: 729-734 [PMID: 18089955]
39 **Cani PD**, Bibiloni R, Knauf C, Waget A, Neyrinck AM, Delzenne NM, Burcelin R. Changes in gut microbiota control metabolic endotoxemia-induced inflammation in high-fat diet-induced obesity and diabetes in mice. *Diabetes* 2008; **57**: 1470-1481 [PMID: 18305141 DOI: 10.2337/db07-1403]
40 **Cani PD**, Amar J, Iglesias MA, Poggi M, Knauf C, Bastelica D, Neyrinck AM, Fava F, Tuohy KM, Chabo C, Waget A, Delmée E, Cousin B, Sulpice T, Chamontin B, Ferrières J, Tanti JF, Gibson GR, Casteilla L, Delzenne NM, Alessi MC, Burcelin R. Metabolic endotoxemia initiates obesity and insulin resistance. *Diabetes* 2007; **56**: 1761-1772 [PMID: 17456850 DOI: 10.2337/db06-1491]
41 **Hazebrouck S**, Przybylski-Nicaise L, Ah-Leung S, Adel-Patient K, Corthier G, Wal JM, Rabot S. Allergic sensitization to bovine beta-lactoglobulin: comparison between germ-free and conventional BALB/c mice. *Int Arch Allergy Immunol* 2009; **148**: 65-72 [PMID: 18716405 DOI: 10.1159/000151507]
42 **Wen L**, Ley RE, Volchkov PY, Stranges PB, Avanesyan L, Stonebraker AC, Hu C, Wong FS, Szot GL, Bluestone JA, Gordon JI, Chervonsky AV. Innate immunity and intestinal microbiota in the development of Type 1 diabetes. *Nature* 2008; **455**: 1109-1113 [PMID: 18806780 DOI: 10.1038/nature07336]
43 **Sudo N**, Chida Y, Aiba Y, Sonoda J, Oyama N, Yu XN, Kubo C, Koga Y. Postnatal microbial colonization programs the hypothalamic-pituitary-adrenal system for stress response in mice. *J Physiol* 2004; **558**: 263-275 [PMID: 15133062 DOI: 10.1113/jphysiol.2004.063388]
44 **Tsuda M**, Hosono A, Yanagibashi T, Kihara-Fujioka M, Hachimura S, Itoh K, Hirayama K, Takahashi K, Kaminogawa

S. Intestinal commensal bacteria promote T cell hyporesponsiveness and down-regulate the serum antibody responses induced by dietary antigen. *Immunol Lett* 2010; **132**: 45-52 [PMID: 20621647 DOI: 10.1016/j.imlet.2010.05.007]

45 **Neufeld KM**, Kang N, Bienenstock J, Foster JA. Reduced anxiety-like behavior and central neurochemical change in germ-free mice. *Neurogastroenterol Motil* 2011; **23**: 255-264, e119 [PMID: 21054680 DOI: 10.1111/j.1365-2982.2010.01620.x]

46 **Pils MC**, Bleich A, Prinz I, Fasnacht N, Bollati-Fogolin M, Schippers A, Rozell B, Müller W. Commensal gut flora reduces susceptibility to experimentally induced colitis via T-cell-derived interleukin-10. *Inflamm Bowel Dis* 2011; **17**: 2038-2046 [PMID: 21182023 DOI: 10.1002/ibd.21587]

47 **Matsumoto S**, Okabe Y, Setoyama H, Takayama K, Ohtsuka J, Funahashi H, Imaoka A, Okada Y, Umesaki Y. Inflammatory bowel disease-like enteritis and caecitis in a senescence accelerated mouse P1/Yit strain. *Gut* 1998; **43**: 71-78 [PMID: 9771408]

48 **Stepankova R**, Powrie F, Kofronova O, Kozakova H, Hudcovic T, Hrncir T, Uhlig H, Read S, Rehakova Z, Benada O, Heczko P, Strus M, Bland P, Tlaskalova-Hogenova H. Segmented filamentous bacteria in a defined bacterial cocktail induce intestinal inflammation in SCID mice reconstituted with CD45RBhigh CD4+ T cells. *Inflamm Bowel Dis* 2007; **13**: 1202-1211 [PMID: 17607724 DOI: 10.1002/ibd.20221]

49 **Amaral FA**, Sachs D, Costa VV, Fagundes CT, Cisalpino D, Cunha TM, Ferreira SH, Cunha FQ, Silva TA, Nicoli JR, Vieira LQ, Souza DG, Teixeira MM. Commensal microbiota is fundamental for the development of inflammatory pain. *Proc Natl Acad Sci USA* 2008; **105**: 2193-2197 [PMID: 18268332 DOI: 10.1073/pnas.0711891105]

50 **Bäckhed F**, Ding H, Wang T, Hooper LV, Koh GY, Nagy A, Semenkovich CF, Gordon JI. The gut microbiota as an environmental factor that regulates fat storage. *Proc Natl Acad Sci USA* 2004; **101**: 15718-15723 [PMID: 15505215 DOI: 10.1073/pnas.0407076101]

51 **Rodriguez B**, Prioult G, Bibiloni R, Nicolis I, Mercenier A, Butel MJ, Waligora-Dupriet AJ. Germ-free status and altered caecal subdominant microbiota are associated with a high susceptibility to cow's milk allergy in mice. *FEMS Microbiol Ecol* 2011; **76**: 133-144 [PMID: 21223329 DOI: 10.1111/j.1574-6941.2010.01035.x]

52 **Breban MA**, Moreau MC, Fournier C, Ducluzeau R, Kahn MF. Influence of the bacterial flora on collagen-induced arthritis in susceptible and resistant strains of rats. *Clin Exp Rheumatol* 1993; **11**: 61-64 [PMID: 8453801]

53 **Taurog JD**, Richardson JA, Croft JT, Simmons WA, Zhou M, Fernández-Sueiro JL, Balish E, Hammer RE. The germfree state prevents development of gut and joint inflammatory disease in HLA-B27 transgenic rats. *J Exp Med* 1994; **180**: 2359-2364 [PMID: 7964509 DOI: 10.1084/jem.180.6.2359]

54 **Contractor NV**, Bassiri H, Reya T, Park AY, Baumgart DC, Wasik MA, Emerson SG, Carding SR. Lymphoid hyperplasia, autoimmunity, and compromised intestinal intraepithelial lymphocyte development in colitis-free gnotobiotic IL-2-deficient mice. *J Immunol* 1998; **160**: 385-394 [PMID: 9551995]

55 **Sadlack B**, Merz H, Schorle H, Schimpl A, Feller AC, Horak I. Ulcerative colitis-like disease in mice with a disrupted interleukin-2 gene. *Cell* 1993; **75**: 253-261 [PMID: 8402910]

56 **Sellon RK**, Tonkonogy S, Schultz M, Dieleman LA, Grenther W, Balish E, Rennick DM, Sartor RB. Resident enteric bacteria are necessary for development of spontaneous colitis and immune system activation in interleukin-10-deficient mice. *Infect Immun* 1998; **66**: 5224-5231 [PMID: 9784526]

57 **Dianda L**, Hanby AM, Wright NA, Sebesteny A, Hayday AC, Owen MJ. T cell receptor-alpha beta-deficient mice fail to develop colitis in the absence of a microbial environment. *Am J Pathol* 1997; **150**: 91-97 [PMID: 9006326]

58 **Schéle E**, Grahnemo L, Anesten F, Hallén A, Bäckhed F, Jansson JO. The gut microbiota reduces leptin sensitivity and the expression of the obesity-suppressing neuropeptides proglucagon (Gcg) and brain-derived neurotrophic factor (Bdnf) in the central nervous system. *Endocrinology* 2013; **154**: 3643-3651 [PMID: 23892476 DOI: 10.1210/en.2012-2151]

59 **Turton MD**, O'Shea D, Gunn I, Beak SA, Edwards CM, Meeran K, Choi SJ, Taylor GM, Heath MM, Lambert PD, Wilding JP, Smith DM, Ghatei MA, Herbert J, Bloom SR. A role for glucagon-like peptide-1 in the central regulation of feeding. *Nature* 1996; **379**: 69-72 [PMID: 8538742 DOI: 10.1038/379069a0]

60 **Neufeld KA**, Kang N, Bienenstock J, Foster JA. Effects of intestinal microbiota on anxiety-like behavior. *Commun Integr Biol* 2011; **4**: 492-494 [PMID: 21966581 DOI: 10.4161/cib.4.4.15702]

61 **Yockey LJ**, Demehri S, Turkoz M, Turkoz A, Ahern PP, Jassim O, Manivasagam S, Kearney JF, Gordon JI, Kopan R. The absence of a microbiota enhances TSLP expression in mice with defective skin barrier but does not affect the severity of their allergic inflammation. *J Invest Dermatol* 2013; **133**: 2714-2721 [PMID: 23698100 DOI: 10.1038/jid.2013.228]

62 **Kaser A**, Zeissig S, Blumberg RS. Inflammatory bowel disease. *Annu Rev Immunol* 2010; **28**: 573-621 [PMID: 20192811 DOI: 10.1146/annurev-immunol-030409-101225]

63 **Kühn R**, Löhler J, Rennick D, Rajewsky K, Müller W. Interleukin-10-deficient mice develop chronic enterocolitis. *Cell* 1993; **75**: 263-274 [PMID: 8402911]

64 **Schultz M**, Tonkonogy SL, Sellon RK, Veltkamp C, Godfrey VL, Kwon J, Grenther WB, Balish E, Horak I, Sartor RB. IL-2-deficient mice raised under germfree conditions develop delayed mild focal intestinal inflammation. *Am J Physiol* 1999; **276**: G1461-G1472 [PMID: 10362650]

65 **Turnbaugh PJ**, Ley RE, Mahowald MA, Magrini V, Mardis ER, Gordon JI. An obesity-associated gut microbiome with increased capacity for energy harvest. *Nature* 2006; **444**: 1027-1031 [PMID: 17183312 DOI: 10.1038/nature05414]

66 **Membrez M**, Blancher F, Jaquet M, Bibiloni R, Cani PD, Burcelin RG, Corthesy I, Macé K, Chou CJ. Gut microbiota modulation with norfloxacin and ampicillin enhances glucose tolerance in mice. *FASEB J* 2008; **22**: 2416-2426 [PMID: 18326786 DOI: 10.1096/fj.07-102723]

67 **Bech-Nielsen GV**, Hansen CH, Hufeldt MR, Nielsen DS, Aasted B, Vogensen FK, Midtvedt T, Hansen AK. Manipulation of the gut microbiota in C57BL/6 mice changes glucose tolerance without affecting weight development and gut mucosal immunity. *Res Vet Sci* 2012; **92**: 501-508 [PMID: 21543097 DOI: 10.1016/j.rvsc.2011.04.005]

68 **Rune I**, Hansen CH, Ellekilde M, Nielsen DS, Skovgaard K, Rolin BC, Lykkesfeldt J, Josefsen K, Tranberg B, Kihl P, Hansen AK. Ampicillin-improved glucose tolerance in diet-induced obese C57BL/6NTac mice is age dependent. *J Diabetes Res* 2013; **2013**: 319321 [PMID: 24369539 DOI: 10.1155/2013/319321]

69 **Cho I**, Yamanishi S, Cox L, Methé BA, Zavadil J, Li K, Gao Z, Mahana D, Raju K, Teitler I, Li H, Alekseyenko AV, Blaser MJ. Antibiotics in early life alter the murine colonic microbiome and adiposity. *Nature* 2012; **488**: 621-626 [PMID: 22914093 DOI: 10.1038/nature11400]

70 **Bonaz BL**, Bernstein CN. Brain-gut interactions in inflammatory bowel disease. *Gastroenterology* 2013; **144**: 36-49 [PMID: 23063970 DOI: 10.1053/j.gastro.2012.10.003]

71 **O'Mahony SM**, Marchesi JR, Scully P, Codling C, Ceolho AM, Quigley EM, Cryan JF, Dinan TG. Early life stress alters behavior, immunity, and microbiota in rats: implications for irritable bowel syndrome and psychiatric illnesses. *Biol Psychiatry* 2009; **65**: 263-267 [PMID: 18723164 DOI: 10.1016/j.biopsych.2008.06.026]

72 **Bravo JA**, Forsythe P, Chew MV, Escaravage E, Savignac HM, Dinan TG, Bienenstock J, Cryan JF. Ingestion of Lactobacillus strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve. *Proc Natl Acad Sci USA* 2011; **108**: 16050-16055 [PMID: 21876150 DOI: 10.1073/pnas.1102999108]

73 **Bangsgaard Bendtsen KM**, Krych L, Sørensen DB, Pang W, Nielsen DS, Josefsen K, Hansen LH, Sørensen SJ, Hansen AK. Gut microbiota composition is correlated to grid floor induced stress and behavior in the BALB/c mouse. *PLoS One* 2012; **7**: e46231 [PMID: 23056268 DOI: 10.1371/journal.pone.0046231]

74 **Dantzer R**, Kelley KW. Twenty years of research on cytokine-induced sickness behavior. *Brain Behav Immun* 2007; **21**: 153-160 [PMID: 17088043 DOI: 10.1016/j.bbi.2006.09.006]

75 **Hanstock TL**, Mallet PE, Clayton EH. Increased plasma d-lactic acid associated with impaired memory in rats. *Physiol Behav* 2010; **101**: 653-659 [PMID: 20888356 DOI: 10.1016/j.physbeh.2010.09.018]

76 **Lundberg R**, Clausen SK, Pang W, Nielsen DS, Möller K, Josefsen KE, Hansen AK. Gastrointestinal microbiota and local inflammation during oxazolone-induced dermatitis in BALB/cA mice. *Comp Med* 2012; **62**: 371-380 [PMID: 23114040]

77 **Zackular JP**, Baxter NT, Iverson KD, Sadler WD, Petrosino JF, Chen GY, Schloss PD. The gut microbiome modulates colon tumorigenesis. *MBio* 2013; **4**: e00692-e00613 [PMID: 24194538 DOI: 10.1128/mBio.00692-13]

78 **Hedlund BP**, Gosink JJ, Staley JT. Verrucomicrobia div. nov., a new division of the bacteria containing three new species of Prosthecobacter. *Antonie Van Leeuwenhoek* 1997; **72**: 29-38 [PMID: 9296261]

79 **Derrien M**, Collado MC, Ben-Amor K, Salminen S, de Vos WM. The Mucin degrader Akkermansia muciniphila is an abundant resident of the human intestinal tract. *Appl Environ Microbiol* 2008; **74**: 1646-1648 [PMID: 18083887 DOI: 10.1128/AEM.01226-07]

80 **Everard A**, Belzer C, Geurts L, Ouwerkerk JP, Druart C, Bindels LB, Guiot Y, Derrien M, Muccioli GG, Delzenne NM, de Vos WM, Cani PD. Cross-talk between Akkermansia muciniphila and intestinal epithelium controls diet-induced obesity. *Proc Natl Acad Sci USA* 2013; **110**: 9066-9071 [PMID: 23671105 DOI: 10.1073/pnas.1219451110]

81 **Marietta EV**, Gomez AM, Yeoman C, Tilahun AY, Clark CR, Luckey DH, Murray JA, White BA, Kudva YC, Rajagopalan G. Low incidence of spontaneous type 1 diabetes in non-obese diabetic mice raised on gluten-free diets is associated with changes in the intestinal microbiome. *PLoS One* 2013; **8**: e78687 [PMID: 24236037 DOI: 10.1371/journal.pone.0078687]

82 **Russell SL**, Gold MJ, Hartmann M, Willing BP, Thorson L, Wlodarska M, Gill N, Blanchet MR, Mohn WW, McNagny KM, Finlay BB. Early life antibiotic-driven changes in microbiota enhance susceptibility to allergic asthma. *EMBO Rep* 2012; **13**: 440-447 [PMID: 22422004 DOI: 10.1038/embor.2012.32]

83 **Engkilde K**, Buschard K, Hansen AK, Menné T, Johansen JD. Prevention of diabetes in NOD mice by repeated exposures to a contact allergen inducing a sub-clinical dermatitis. *PLoS One* 2010; **5**: e10591 [PMID: 20485668 DOI: 10.1371/journal.pone.0010591]

84 **Engkilde K**, Johansen JD, Hansen AK, Menné T, Buschard K. Prevention of type 1 diabetes by inducing subclinical dermatitis on a small area. *Diabetes Metab Res Rev* 2011; **27**: 954-958 [PMID: 22069292 DOI: 10.1002/dmrr.1280]

85 **Kang CS**, Ban M, Choi EJ, Moon HG, Jeon JS, Kim DK, Park SK, Jeon SG, Roh TY, Myung SJ, Gho YS, Kim JG, Kim YK. Extracellular vesicles derived from gut microbiota, especially Akkermansia muciniphila, protect the progression of dextran sulfate sodium-induced colitis. *PLoS One* 2013; **8**: e76520 [PMID: 24204633 DOI: 10.1371/journal.pone.0076520]

86 **Ganesh BP**, Klopfleisch R, Loh G, Blaut M. Commensal Akkermansia muciniphila exacerbates gut inflammation in Salmonella Typhimurium-infected gnotobiotic mice. *PLoS One* 2013; **8**: e74963 [PMID: 24040367 DOI: 10.1371/journal.pone.0074963]

87 **Hansen CH**, Holm TL, Krych Ł, Andresen L, Nielsen DS, Rune I, Hansen AK, Skov S. Gut microbiota regulates NKG2D ligand expression on intestinal epithelial cells. *Eur J Immunol* 2013; **43**: 447-457 [PMID: 23136011 DOI: 10.1002/eji.201242462]

88 **Kuwahara T**, Ogura Y, Oshima K, Kurokawa K, Ooka T, Hirakawa H, Itoh T, Nakayama-Imaohji H, Ichimura M, Itoh K, Ishifune C, Maekawa Y, Yasutomo K, Hattori M, Hayashi T. The lifestyle of the segmented filamentous bacterium: a non-culturable gut-associated immunostimulating microbe inferred by whole-genome sequencing. *DNA Res* 2011; **18**: 291-303 [PMID: 21791478 DOI: 10.1093/dnares/dsr022]

89 **Margulis L**, Jorgensen JZ, Dolan S, Kolchinsky R, Rainey FA, Lo SC. The Arthromitus stage of Bacillus cereus: intestinal symbionts of animals. *Proc Natl Acad Sci USA* 1998; **95**: 1236-1241 [PMID: 9448315]

90 **Ivanov II**, Littman DR. Segmented filamentous bacteria take the stage. *Mucosal Immunol* 2010; **3**: 209-212 [PMID: 20147894 DOI: 10.1038/mi.2010.3]

91 **Ivanov II**, Atarashi K, Manel N, Brodie EL, Shima T, Karaoz U, Wei D, Goldfarb KC, Santee CA, Lynch SV, Tanoue T, Imaoka A, Itoh K, Takeda K, Umesaki Y, Honda K, Littman DR. Induction of intestinal Th17 cells by segmented filamentous bacteria. *Cell* 2009; **139**: 485-498 [PMID: 19836068 DOI: 10.1016/j.cell.2009.09.033]

92 **Ivanov II**, Frutos Rde L, Manel N, Yoshinaga K, Rifkin DB, Sartor RB, Finlay BB, Littman DR. Specific microbiota direct the differentiation of IL-17-producing T-helper cells in the mucosa of the small intestine. *Cell Host Microbe* 2008; **4**: 337-349 [PMID: 18854238 DOI: 10.1016/j.chom.2008.09.009]

93 **Kriegel MA**, Sefik E, Hill JA, Wu HJ, Benoist C, Mathis D. Naturally transmitted segmented filamentous bacteria segregate with diabetes protection in nonobese diabetic mice. *Proc Natl Acad Sci USA* 2011; **108**: 11548-11553 [PMID: 21709219 DOI: 10.1073/pnas.1108924108]

94 **Balish E**, Warner T. Enterococcus faecalis induces inflammatory bowel disease in interleukin-10 knockout mice. *Am J Pathol* 2002; **160**: 2253-2257 [PMID: 12057927 DOI: 10.1016/S0002-9440(10)61172-8]

95 **Kim SC**, Tonkonogy SL, Albright CA, Tsang J, Balish EJ, Braun J, Huycke MM, Sartor RB. Variable phenotypes of enterocolitis in interleukin 10-deficient mice monoassociated with two different commensal bacteria. *Gastroenterology* 2005; **128**: 891-906 [PMID: 15825073]

96 **Steck N**, Hoffmann M, Sava IG, Kim SC, Hahne H, Tonkonogy SL, Mair K, Krueger D, Pruteanu M, Shanahan F, Vogelmann R, Schemann M, Kuster B, Sartor RB, Haller D. Enterococcus faecalis metalloprotease compromises epithelial barrier and contributes to intestinal inflammation. *Gastroenterology* 2011; **141**: 959-971 [PMID: 21699778 DOI: 10.1053/j.gastro.2011.05.035]

97 **Duncan SH**, Hold GL, Harmsen HJ, Stewart CS, Flint HJ. Growth requirements and fermentation products of Fusobacterium prausnitzii, and a proposal to reclassify it as Faecalibacterium prausnitzii gen. nov., comb. nov. *Int J Syst Evol Microbiol* 2002; **52**: 2141-2146 [PMID: 12508881]

98 **Sokol H**, Pigneur B, Watterlot L, Lakhdari O, Bermúdez-Humarán LG, Gratadoux JJ, Blugeon S, Bridonneau C, Furet JP, Corthier G, Grangette C, Vasquez N, Pochart P, Trugnan G, Thomas G, Blottière HM, Doré J, Marteau P, Seksik P, Langella P. Faecalibacterium prausnitzii is an anti-inflammatory commensal bacterium identified by gut microbiota analysis of Crohn disease patients. *Proc Natl Acad Sci USA* 2008; **105**: 16731-16736 [PMID: 18936492 DOI: 10.1073/pnas.0804812105]

99 **Paturi G**, Mandimika T, Butts CA, Zhu S, Roy NC, McNabb WC, Ansell J. Influence of dietary blueberry and broccoli on cecal microbiota activity and colon morphology in mdr1a(-/-) mice, a model of inflammatory bowel diseases. *Nutrition* 2012; **28**: 324-330 [PMID: 22113065 DOI: 10.1016/j.nut.2011.07.018]

100 **Carlsson AH**, Yakymenko O, Olivier I, Håkansson F, Postma E, Keita AV, Söderholm JD. Faecalibacterium prausnitzii supernatant improves intestinal barrier function in mice DSS colitis. *Scand J Gastroenterol* 2013; **48**: 1136-1144 [PMID: 23971882 DOI: 10.3109/00365521.2013.828773]

101 **Hansen CH**, Frøkiær H, Christensen AG, Bergström A, Licht TR, Hansen AK, Metzdorff SB. Dietary xylooligosaccharide downregulates IFN-γ and the low-grade inflammatory cy-

tokine IL-1β systemically in mice. *J Nutr* 2013; **143**: 533-540 [PMID: 23427328 DOI: 10.3945/jn.112.172361]
102 **Lam V**, Su J, Koprowski S, Hsu A, Tweddell JS, Rafiee P, Gross GJ, Salzman NH, Baker JE. Intestinal microbiota determine severity of myocardial infarction in rats. *FASEB J* 2012; **26**: 1727-1735 [PMID: 22247331 DOI: 10.1096/fj.11-197921]
103 **McCarthy J**, O'Mahony L, O'Callaghan L, Sheil B, Vaughan EE, Fitzsimons N, Fitzgibbon J, O'Sullivan GC, Kiely B, Collins JK, Shanahan F. Double blind, placebo controlled trial of two probiotic strains in interleukin 10 knockout mice and mechanistic link with cytokine balance. *Gut* 2003; **52**: 975-980 [PMID: 12801954]
104 **Schwarzer M**, Srutkova D, Schabussova I, Hudcovic T, Akgün J, Wiedermann U, Kozakova H. Neonatal colonization of germ-free mice with Bifidobacterium longum prevents allergic sensitization to major birch pollen allergen Bet v 1. *Vaccine* 2013; **31**: 5405-5412 [PMID: 24055352 DOI: 10.1016/j.vaccine.2013.09.014]
105 **Brinkman BM**, Becker A, Ayiseh RB, Hildebrand F, Raes J, Huys G, Vandenabeele P. Gut microbiota affects sensitivity to acute DSS-induced colitis independently of host genotype. *Inflamm Bowel Dis* 2013; **19**: 2560-2567 [PMID: 24105395 DOI: 10.1097/MIB.0b013e3182a8759a]
106 **Rath HC**, Wilson KH, Sartor RB. Differential induction of colitis and gastritis in HLA-B27 transgenic rats selectively colonized with Bacteroides vulgatus or Escherichia coli. *Infect Immun* 1999; **67**: 2969-2974 [PMID: 10338507]
107 **Brugman S**, Klatter FA, Visser JT, Wildeboer-Veloo AC, Harmsen HJ, Rozing J, Bos NA. Antibiotic treatment partially protects against type 1 diabetes in the Bio-Breeding diabetes-prone rat. Is the gut flora involved in the development of type 1 diabetes? *Diabetologia* 2006; **49**: 2105-2108 [PMID: 16816951 DOI: 10.1007/s00125-006-0334-0]
108 **Xu J**, Mahowald MA, Ley RE, Lozupone CA, Hamady M, Martens EC, Henrissat B, Coutinho PM, Minx P, Latreille P, Cordum H, Van Brunt A, Kim K, Fulton RS, Fulton LA, Clifton SW, Wilson RK, Knight RD, Gordon JI. Evolution of symbiotic bacteria in the distal human intestine. *PLoS Biol* 2007; **5**: e156 [PMID: 17579514 DOI: 10.1371/journal.pbio.0050156]
109 **Martens EC**, Chiang HC, Gordon JI. Mucosal glycan foraging enhances fitness and transmission of a saccharolytic human gut bacterial symbiont. *Cell Host Microbe* 2008; **4**: 447-457 [PMID: 18996345 DOI: 10.1016/j.chom.2008.09.007]
110 **Nakano V**, Gomes DA, Arantes RM, Nicoli JR, Avila-Campos MJ. Evaluation of the pathogenicity of the Bacteroides fragilis toxin gene subtypes in gnotobiotic mice. *Curr Microbiol* 2006; **53**: 113-117 [PMID: 16832728 DOI: 10.1007/s00284-005-0321-6]
111 **Wu S**, Rhee KJ, Albesiano E, Rabizadeh S, Wu X, Yen HR, Huso DL, Brancati FL, Wick E, McAllister F, Housseau F, Pardoll DM, Sears CL. A human colonic commensal promotes colon tumorigenesis via activation of T helper type 17 T cell responses. *Nat Med* 2009; **15**: 1016-1022 [PMID: 19701202 DOI: 10.1038/nm.2015]
112 **Mazmanian SK**, Round JL, Kasper DL. A microbial symbiosis factor prevents intestinal inflammatory disease. *Nature* 2008; **453**: 620-625 [PMID: 18509436 DOI: 10.1038/nature07008]
113 **Hsiao EY**, McBride SW, Hsien S, Sharon G, Hyde ER, McCue T, Codelli JA, Chow J, Reisman SE, Petrosino JF, Patterson PH, Mazmanian SK. Microbiota modulate behavioral and physiological abnormalities associated with neurodevelopmental disorders. *Cell* 2013; **155**: 1451-1463 [PMID: 24315484 DOI: 10.1016/j.cell.2013.11.024]
114 **Ukena SN**, Singh A, Dringenberg U, Engelhardt R, Seidler U, Hansen W, Bleich A, Bruder D, Franzke A, Rogler G, Suerbaum S, Buer J, Gunzer F, Westendorf AM. Probiotic Escherichia coli Nissle 1917 inhibits leaky gut by enhancing mucosal integrity. *PLoS One* 2007; **2**: e1308 [PMID: 18074031 DOI: 10.1371/journal.pone.0001308]
115 **Turroni F**, Taverniti V, Ruas-Madiedo P, Duranti S, Guglielmetti S, Lugli GA, Gioiosa L, Palanza P, Margolles A, van Sinderen D, Ventura M. Bifidobacterium bifidum PRL2010 modulates the host innate immune response. *Appl Environ Microbiol* 2014; **80**: 730-740 [PMID: 24242237 DOI: 10.1128/AEM.03313-13]
116 **Hufeldt MR**, Nielsen DS, Vogensen FK, Midtvedt T, Hansen AK. Family relationship of female breeders reduce the systematic inter-individual variation in the gut microbiota of inbred laboratory mice. *Lab Anim* 2010; **44**: 283-289 [PMID: 20713427 DOI: 10.1258/la.2010.010058]
117 **Pang W**, Stradiotto D, Krych L, Karlskov-Mortensen P, Vogensen FK, Nielsen DS, Fredholm M, Hansen AK. Selective inbreeding does not increase gut microbiota similarity in BALB/c mice. *Lab Anim* 2012; **46**: 335-337 [PMID: 23097567 DOI: 10.1258/la.2012.012040]
118 **Hansen CH**, Metzdorff SB, Hansen AK. Customizing laboratory mice by modifying gut microbiota and host immunity in an early "window of opportunity". *Gut Microbes* 2013; **4**: 241-245 [PMID: 23549457 DOI: 10.4161/gmic.23999]

P- Reviewer: Bailey MT, Franceschi F
S- Editor: Nan J **L- Editor**: Stewart G **E- Editor**: Liu XM

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

ISSN 1007-9327