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REVIEW ARTICLE

WILEY Helicobacter

Other Helicobacters, gastric and gut microbiota

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Abstract

The current article is a review of the most important and relevant literature published in 2016 and early 2017 on non-*Helicobacter pylori* Helicobacter infections in humans and animals, as well as interactions between *H. pylori* and the microbiota of the stomach and other organs. Some putative new *Helicobacter* species were identified in sea otters, wild boars, dogs, and mice. Many cases of *Helicobacter fennelliae* and *Helicobacter cinaedi* infection have been reported in humans, mostly in immunocompromised patients. Mouse models have been used frequently as a model to investigate human Helicobacter infection, although some studies have investigated the pathogenesis of Helicobacters in their natural host, as was the case for *Helicobacter suis* infection in pigs. Our understanding of both the gastric and gut microbiome has made progress and, in addition, interactions between *H. pylori* and the microbiome were demonstrated to go beyond the stomach. Some new approaches of preventing Helicobacter infection or its related pathologies were investigated and, in this respect, the probiotic properties of *Saccharomyces*, *Lactobacillus* and *Bifidobacterium* spp. were confirmed.

KEYWORDS

H. cinaedi, microbiome, non *Helicobacter pylori* Helicobacters, pathogenesis, taxonomy

1 | TAXONOMY, PREVALENCE, AND DIAGNOSIS OF NON-*HELICOBACTER PYLORI* HELICOBACTER (NHPH) INFECTION

To date, 37 *Helicobacter* species have been validated. In 2016, some new species were proposed as candidates to be added to the growing *Helicobacter* genus. "*Helicobacter enhydrae*" sp. nov. was isolated from the inflamed stomach of southern sea otters.[1] A 16S and 23S rRNA gene sequence analysis showed that it is closely related to *Helicobacter mustelae*, colonizing the stomach of ferrets. A striking difference between the two species is the fact that *H. mustelae* is urease-positive, whereas "*H. enhydrae*" lacks this enzyme which is crucial for gastric colonization.[2] Another novel urease-negative *Helicobacter* species, "*Helicobacter apri*" sp. nov., was isolated from the stomach and cecal contents of wild boars living in the Apennine Mountains.[3] "*Helicobacter canicola*" sp. nov., isolated from canine feces, was previously misidentified as *Helicobacter cinaedi*. However, it exhibited different biochemical traits and phylogenetic analyses (16S rRNA, 23S rRNA, *gyrB*, and *hsp60* gene sequences), confirmed that this bacterium form a distinct cluster.[4] A putative novel *Helicobacter* species, "*Helicobacter japonicum*" sp. nov., was isolated from the stomach and intestines of clinically normal mice. This bacillus exhibits in vitro cytolethal distending toxin (CDT) activity and induces the development of inflammatory bowel disease and carcinoma in C57BL/129 IL10$^{-/-}$ mice.[5] Rimbara et al.[6] corrected the draft genome sequence of *Helicobacter fennelliae* strain MRY12-0050, isolated from a patient with bacteremia. Indeed, a putative CDT gene cluster was identified, with the gene products sharing 31%, 36%, and 32% amino acid sequence identity with CdtA, CdtB, and CdtC of *H. cinaedi* strain CCUG 18818, respectively.[7]

Most cats carry Helicobacters in their stomach,[8] a finding which was confirmed in a recent study in Japan. Kubota-Aizawa et al. showed that half of the cats tested were infected with a non-*H. pylori* Helicobacter (NHPH), of which *Helicobacter heilmannii* sensu stricto (s.s.). was the most prevalent species, followed by *Helicobacter felis*

and *Helicobacter bizzozeronii*. Also in this study, no clear correlation was found between infection and gastritis, although gastric carcinoma was observed in a cat infected with *H. heilmannii* s.s.[9] Although it should be noted that the authors did not test for all carnivore *Helicobacter* species, Hong et al.[10] described a case of *H. felis* infection in a 3 month-old kitten from a research facility, suffering from anorexia and occasional vomiting. The prevalence of enterohepatic *Helicobacter* sp. in cats with nonhematopoietic intestinal carcinoma (55 cases) was shown to be as high as 56%, and one or more species-specific assays were positive for *Helicobacter bilis*, *Helicobacter canis*, or *Helicobacter marmotae*. The presence of NHPH was significantly associated with large intestinal carcinoma (68%) and mucinous adenocarcinoma (92%).[11] Sabry et al. evaluated 149 animals and 10 human fecal samples for the presence of *Helicobacter* sp. based on 16S rRNA gene analysis. NHPH prevalence was 14.8%, while the distribution among the different animals: sheep, goat, and cattle, was 26.3%, 3%, and 4.8% respectively. *Helicobacter canis* was the predominant species detected only in sheep (21%) and goats (3%). Moreover, "*Helicobacter winghamensis*" and *Helicobacter canadensis* were also detected in sheep but not in other animals. In humans, four of 10 patients were positive and all sequences were identified as *H. canis*. One of these sequences was identical to that of sheep and suggested the zoonotic transmission of this pathogen between sheep and humans.[12] *Helicobacter trogontum* and *H. bilis* were isolated from the livers of aborted sheep fetuses in 20% of cases.[13]

Many cases of NHPH infection in humans were reported this year, mainly *H. fennelliae* and *H. cinaedi* in immunocompromised patients. *H. fennelliae* bacteremia was observed in a 73-year-old Japanese man, suffering from lung adenocarcinoma and treated by platinum-based chemotherapy. Despite antibiotic therapy (cefepime, amoxicillin, and doxycycline for 6 weeks), the bacteremia reoccurred, most likely due to the long-term damage of the enteric mucosa by platinum-based drugs. The man was ultimately treated by selective digestive decontamination with kanamycin.[14] Saito et al.[15] reported three new cases of *H. fennelliae* bacteremia with gastrointestinal symptoms (nausea, vomiting, and diarrhea), and a retrospective study of 24 cases of *H. fennelliae* bacteremia reported in the literature showed that most of the patients had a background of immunosuppression, including solid tumors, hematological malignancies, and autoimmune diseases. A 54-year-old man, who underwent a kidney transplant 14 years ago and suffered from fever and multifocal cellulitis, was shown to be infected by *H. cinaedi*, which was eradicated by 6 weeks of antibiotic therapy.[16] A 40-year-old woman with systemic lupus erythematosus presented with high-grade fever and severe thrombocytopenia, suggesting a complication of her disease, and she was finally diagnosed with *H. cinaedi* bacteremia.[17] In another case report, a 52-year-old Japanese man with a persistent headache and suspected intracranial subdural empyema was diagnosed with *H. cinaedi* bacteremia treated by two neurosurgical drainages and 4 weeks of meropenem treatment.[18] The first case of cerebral cyst infection by *H. cinaedi* was reported in a 70 year-old man who had a persisting fever for 2 weeks prior to hospital admission. An Ommaya reservoir was inserted in a cerebral cyst secondary to radiotherapy for parapharyngeal space squamous cell carcinoma 10 years before.[19] *Helicobacter cinaedi* was also identified in aortic specimen samples from a 49 year-old man with an implantable left ventricular assist device who presented with the complication of a ruptured infective common iliac aneurysm,[20] in another 49 year-old man with multiple myeloma and autologous stem cell transplantation who had febrile diarrhea and malakoplakia,[21] in the urine of a 77 year-old man on hemodialysis admitted for feverishness and penile pain with urination,[22] and in a 38 year-old Japanese man with X-linked agammaglobulinemia complicated by recurrent cellulitis for 2 years.[23] Another patient with agammaglobulinemia had a refractory bacteremia with fever and erythema extended to both legs, caused by *H. cinaedi*, which was resistant to penicillins and cephalosporins during prolonged treatment. Intravenous treatment with imipenem/cilastatin and minocycline for 2 weeks pursued by oral minocycline for 2 months eliminated symptoms, although a stool sample was still positive for *H. cinaedi*.[24] A 54-year-old immunocompetent Japanese man who was found to have bacteremia complicated with bilateral lower extremity cellulitis due to *H. cinaedi* had two recurring episodes post-treatment; therefore, treatment was prolonged (12 weeks) until his symptoms subsided.[25] The *H. cinaedi* cinaedi atherosclerosis inflammatory protein (CAIP) antigen participates in atherosclerotic inflammation by promoting macrophage differentiation into foam cells and drives a pro-inflammatory Th1 phenotype, an immunopathological response associated with atherosclerosis.[26] Schmitz et al.[27] showed that in vitro growth of *H. cinaedi* could be enhanced by coculture with human epithelial cells (Caco-2, LS-174T, AGS, and HeLa) and L-lactate supplementation under H_2-free aerobic conditions.

Diagnosis of *Helicobacter suis* infection is often problematic, mainly due to the extremely difficult isolation of this bacterium. Indeed, in vitro isolation of *H. suis* from infected humans has so far been unsuccessful and the few human isolates available have always been maintained in vivo via mouse passaging. Interestingly, Matsui et al.,[28] for the first time, determined the whole-genome sequence from a mouse-passaged *H. suis* strain, obtained from a Japanese patient with nodular gastritis. In contrast to some other *Helicobacter* species, different gastric NHPH species cannot be easily identified by mere 16SrRNA gene sequence analysis; this was confirmed by Puri et al.[29] who analyzed hundreds of *Helicobacter* 16S rRNA gene sequences from 45 different *Helicobacter* species. Detection of *H. suis* infection in humans has thus far only been possible by molecular methods, but the available PCR assays occasionally cross-react with host DNA or DNA from other *Helicobacter* species. Blaecher et al.[30] developed a highly sensitive and specific probe-based RT-PCR assay and an optimized protocol to isolate low numbers of *H. suis* from infected mice. Both methods may help to detect and isolate *H. suis* from humans in the future. Detection of *H. suis* and other gastric NHPH in gastric tissue is also possible in routine histology and immunohistochemistry, although not up to the species level. Fernandez-Flores et al.[31] demonstrated that an anti-*Treponema* antibody also stains gastric NHPH. This cross-reactivity indicates that immunohistochemical staining results should be interpreted with caution. A method was developed to

identify five enterohepatic *Helicobacter* species (*H. bilis*, *Helicobacter rodentium*, *Helicobacter muridarum*, *Helicobacter typhlonius*, and *Helicobacter hepaticus*) with nested PCR followed by high-resolution melting curve analysis.[32]

2 | PATHOGENESIS OF NON *HELICOBACTER PYLORI* HELICOBACTER INFECTIONS

For a long time, the lack of *H. suis* in vitro culture has hampered research on the pathogenesis of infection. Recently, *H. suis* strains were isolated in vitro from the stomach of rhesus monkeys and crab-eating macaques. Similar to pig-associated *H. suis* strains,[33] these primate-associated *H. suis* strains were shown to induce severe gastric inflammation in mice and Mongolian gerbils, which was accompanied by a marked Th17 response and increased CXCL-13 levels, which may play a role in the development of typical lymphoid lesions associated with *H. suis* infection.[34] These same authors characterized, for the first time, the inflammation in the stomach of *H. suis*-infected pigs.[35] Similar to the mouse model, increased IL-17 expression levels were observed in infected animals. In contrast to mice, however, stimulation with *H. suis* resulted in semi-maturation of moDC, which skewed the immune response toward a Treg-biased response. Previous studies have shown that *H. suis* not only induces an immune response, but also interacts with gastric epithelium. Zhang et al.[36] showed that this bacterium closely interacts with porcine gastric acid-producing parietal cells, affecting the health as well as the function of this cell type.

To understand how *H. cinaedi* could be translocated after passage through the intestinal mucosa and induced bacteremia, a preclinical animal model was developed. Male BALB/c mice were inoculated orally with a human *H. cinaedi* strain. The organism persistently colonized (at least 56 days) the mouse intestinal tracts, particularly the cecum and colon. The inoculated bacteria were recovered from the spleen, liver, kidneys, lungs, bladder, and mesenteric lymph nodes during the first 2 weeks of bacteremia, but not after 4 weeks.[37]

Helicobacter hepaticus colonization is substantially increased in the ileum of BALB/c mice with vitamin D deficiency and high fat feeding. Oral administration of alpha 5 defensin restored eubiosis and showed eradication of *H. hepaticus*.[38]

Helicobacter bilis infection of C3H/HeN mice harboring the altered Schaedler flora (ASF) induced the development of colitis associated with temporal changes in composition and spatial distribution of the mucosal microbiota. Adherent biofilms in colitic mice were composed of total bacteria, ASF457, and *H. bilis* in the majority of samples.[39]

Various mouse models were implemented to investigate NHPH infection. Male lamellipodin KO mice, infected with *Helicobacter* species (mainly by *H. typhlonius* and *H. hepaticus*), developed rectal prolapse and lesions consistent with invasive rectal carcinoma unlike uninfected mice.[40] In 129/SvEv RAG2$^{-/-}$ mice, the CDT of *H. hepaticus* was not involved in cecal colonization but increased the severity of cecal pathology: preneoplastic dysplasia progressed to cancer after 10 to 20 weeks postinfection. The CDT increased the number of lower bowel intestinal γH2AX-positive epithelial cells (a double-stranded DNA break marker) and transcriptional upregulation of cecal TNFα and IL-6 was also observed, as well as phospho-STAT3 foci^{+} intestinal crypts, suggesting that CDT promotes *H. hepaticus* carcinogenesis by enhancing DNA breaks and activation of the TNFα/IL-6-STAT3 signaling pathway.[41] To examine whether conversion of Th17 cells into Th1-like cells is necessary for immunopathology, a *H. hepaticus* typhlocolitis model was used. In C57BL/6J IL17A^{Cre} or RAG1^{Cre} mice, no Th1-like IFNγ^{+} ex-Th17 cells were induced during *H. hepaticus* infection. Despite the lack of these cells, the degree of *H. hepaticus*-triggered intestinal inflammation in mice did not differ from control mice.[42] *Helicobacter hepaticus*-infected C57BL/6 RAG$^{-/-}$CD11c^{cre}IL10RA$^{fl/fl}$ mice with a CD11c-specific deletion of the IL-10 receptor alpha developed severe large intestinal inflammation with infiltrating T cells and increased levels of IL-17a, IFNγ, and IL-12p40. These results demonstrate that IL-10 control of CD11c+ myeloid cells is essential to the maintenance of immune homeostasis in the small and large intestine and protection against *H. hepaticus*-induced colitis.[43] *Helicobacter hepaticus* infection of RAG2-deficient mice induces high levels of IL-22,[44] as well as the expression of iNOS and the development of DNA double-stranded breaks, depending on iNOS activity, especially in proliferating crypt epithelial cells, and development of dysplasia. Depletion of the *H. hepaticus*-induced cytokine IL-22 inhibited these effects.[45]

3 | *HELICOBACTER FELIS* INFECTION OF MICE AS A MODEL FOR HUMAN *H. PYLORI* INFECTION

In the past, experimental infection of mice with *H. felis* was often used as a surrogate model for human *Helicobacter (pylori)* infection, and this was also the case in 2016. In line with what Bosschem et al. showed for *H. suis*,[34] Chonwerawong et al.[46] found that the host background has a profound impact on the susceptibility to Helicobacter-induced pathologies. In a Th2-polarized BALB/c mouse model, the Th1 cytokine IFN-γ was shown not to be required for host defense against experimental *H. felis* infection, although it was important for lymphoid aggregate formation.

Experimental infection of mice on a Th1-prone C57BL/6 background with *H. felis* is often performed to study Helicobacter-induced carcinogenesis. *Helicobacter felis*-infected Myd88$^{-/-}$ mice previously showed an accelerated progression to gastric dysplasia compared to wild-type mice.[47] Global transcriptome analysis in the same mouse model revealed upregulation of chitinase-like 4, involved in tissue remodeling and wound healing, as well as other genes involved in gastric cancer progression.[48]

Nardilysin is a metalloendopeptidase promoting ectodomain shedding of various growth factors and cytokines. Kimura et al.[49] showed that deletion of nardilysin in mice with a CBA background resulted in attenuation of metaplastic changes induced by *H. felis* infection, most likely due to the profound role of nardilysin, in regulating gastric inflammation.

4 | TREATMENT AND PREVENTION OF NON *HELICOBACTER PYLORI* HELICOBACTER INFECTIONS

The search for new therapeutics targeting *Helicobacter* sp. and related gastric pathologies also continued in 2016. Hexane extracts of *Callophylum brasiliense*, an evergreen tree native to Latin America's rain forests, were shown to attenuate *H. felis*-induced gastric epithelial pathology,[50] and crude *N*-acetylneuraminic acid obtained from glycomacropeptide (G-NANA) of whey was shown to possess anti-*Helicobacter* activity, reducing *H. felis* colonization levels in mice.[51] Administration of *Saccharomyces boulardii* to *H. suis*-infected mice resulted in increased *H. suis*-specific IgA levels in gastric juice, lower bacterial colonization levels, and reduced formation of gastric lymphoid follicles, which are typically induced by chronic *H. suis* infection.[52]

Some NHPH, in particular "*Helicobacter apodemus*," *Helicobacter cholecystus*, and *H. rodentium*, were significantly more abundant during pregnancy of Sprague Dawley rats. Antibiotic treatment (azithromycin or cefaclor) significantly reduced the relative abundance of Helicobacters, and the effect was more marked in non-pregnant animals.[53] In mice with a deficiency in intestinal proteoglycan (mucin2), the classic triple antibiotic therapy (amoxicillin, clarithromycin, and metronidazole) had negative effects on reproductive performance and could not eradicate NHPH while in vitro fertilization with embryo transfer was effective.[54] All 11 *Helicobacter pullorum* isolates from broiler and free-range chickens sampled from retail wet markets were resistant to multiple antibiotic classes, that is, fluoroquinolones, cephalosporins, sulfonamides, macrolides, and clavulanic acid. Comparative genomic analysis of these isolates revealed the presence of antimicrobial resistance genes, a significant prevalence of prophages, and the presence of genomic islands.[55] Three new *Helicobacter* prophages were identified in *H. hepaticus* (ATCC 51449), *Helicobacter cetorum* (MIT 99-5656), and *H. bizzozeronii* (CIII-1). The prophage phiHBZC1_1 of *H. bizzozeronii* harbors a gene highly similar to *emrD* encoding the multidrug resistance protein D of *Salmonella enterica* subsp. *enterica* serovar Infantis.[56] NHPH isolates from cheese, milk, milking equipment, tanks, cheese ripening chambers, and sinks in small enterprises involved in the production of cow's milk and the manufacture of goat cheese, showed biocide tolerance and had a sulfonamide resistance gene.[57] The abundance of Helicobacters was significantly increased after 2 weeks of a lactulose treatment, mainly in the cecal mucus (72%) in C57BL/6J mice.[58] Also, the quest for an *H. pylori* vaccine is ongoing. Using an *H. felis* and *H. pylori* mouse model, Moyat et al.[59] showed that IL-22 has a critical role in vaccine-induced protection. This effect was shown not to depend on the pro-inflammatory properties of IL-22, but rather on the increased expression of antimicrobial peptides, such as RegIIIb, capable of killing Helicobacter. Future research should determine the true value of these potential novel strategies for the prevention and treatment of *Helicobacter* infection-related diseases and should continue to focus on the emergence of antimicrobial resistance.

5 | GASTRIC AND GUT MICROBIOTA

The application of high-throughput next-generation sequencing (NGS) has spearheaded the study of the human gastric microbiome to enhance our understanding of the microbiota residing in our stomach. It is now established that the human stomach is a niche environment colonized by specialized and unique gastric microbiota represented by Proteobacteria, Firmicutes, Actinobacteria, Bacteroidetes, and Fusobacteria as the major phyla in both adults and children.[60-62] Among *H. pylori*-positive patients, this species dominates the mucosa-associated microbiota.[62,63] However, the role of conventional culturing techniques in the studying of gastric microbiota should also not be undermined. Indeed, besides *H. pylori*, bacteria belonging to various genera have been isolated in vitro from gastric juice or gastric mucosa. These include *Streptococcus* spp., *Neisseria* spp., *Klebsiella* spp., *Lactobacillus* spp., *Escherichia coli*, *Rothia* sp., *Burkholderia pseudomallei*, *Bacillus* sp., *Morganella morganii*, *Acinetobacter* sp., *Haemophilus* sp., *Veillonella* sp., *Clostridium* sp., *Bacteroides* sp., *Corynebacterium* sp., and *Peptococcus* sp.[63-65] Recently, a strain of a Gram-positive, facultative anaerobic and nonmotile coccus isolated from gastric lavage of a patient was sequenced. Based on phenotypic and genomic analysis, the validation of *Streptococcus timonensis* as a new member of the *Streptococcus* genus has been proposed.[66] Actual isolation of microbial members of the human gastric microbiota enables in vitro and in vivo studies to be carried out to extend our knowledge of the gastric microbiota.

Studying monozygotic twins provides a unique opportunity to determine whether the gastric microbiome is influenced more heavily by genetics or by the environment. Analysis of the gastric microbiome of four pairs of monozygotic twins with dyspepsia and eight gender- and age-matched unrelated individuals from Qingdao (China) demonstrated interpersonal variations in richness and evenness even among co-twins with a similar genetic background. Thus, exogenous factors (such as diet, medication, lifestyle, and environment) rather than host genetic factors may play more important roles in shaping the gastric microbiome of individuals.[67]

Several studies investigated the effects of *H. pylori* on the gastric microbiome in symptomatic pediatric patients. A study characterized the gastric microbiome of 51 pediatric patients with dyspeptic symptoms (18 *H. pylori* positive and 33 negative) from Madrid, Spain.[62] Brawner et al. compared 45 children and 41 adults with chronic symptoms and *H. pylori* infection in Santiago (Chile) and showed that the overall gastric microbiota composition of *H. pylori*-positive children differed significantly from that of *H. pylori*-negative children and that of adults (regardless of *H. pylori* status).[68] Therefore, acquisition of *H. pylori* early in life might have played a bigger role in shaping our gastric microbiome composition than acquiring the bacterium later in life.

Beyond taxonomical knowledge, it is at least as important to understand functions of the interaction between *H. pylori* and the gastric microbiome. Brawner et al.[68] further reported that, in *H. pylori*-positive children, *FOXP3*, *IL-10*, and *TGFβ* expressions were elevated and this is consistent with increased Treg cell responses, which is important for

differentiating between self and foreign antigens. Thus, *H. pylori* might persist in the stomach during early life by promoting immunological tolerance and downregulating gastric inflammation, which is consistent with reduced gastric disease severity in *H. pylori*-positive children compared to *H. pylori*-positive adults. Liquid chromatography-coupled tandem mass spectrometry-based proteomics was used to study the interactions between *H. pylori* and members of the gastric microbiota or host environment. Khosravi et al.[69] demonstrated interactions between *H. pylori* and *Streptococcus mitis*, which is commonly found in the human stomach. By analyzing the proteome along different sites of the gastrointestinal tract (including the stomach) of germ-free, *Bacteroides thetaiotaomicron* monocolonized and conventionally raised mice, Lichtman et al.[70] showed that the presence of gut microbiota substantially impacted the proteomic profile of the stomach of mice. Unlike most studies of similar nature that rely on sequencing variable regions of 16S rRNA gene, Schulz et al. used a reverse-transcribed 16S rRNA gene that has the advantage of capturing only transcriptionally active bacteria. In 24 adult patients from Germany, it was found that the presence of *H. pylori* exerts significant influences on the microbiome of duodenum and oral cavity and consequently may influence the development of duodenal diseases.[63]

In addition to *H. pylori*, recent studies implied that *Streptococcus* sp. and *Prevotella* sp. may also be functionally active in the gastric microbiota. The effect of omeprazole, a proton-pump inhibitor (PPI) commonly used as part of anti-*H. pylori* eradication regimens, on the gastric microbiome was studied. Notably, Firmicutes, particularly *Streptococcus* sp., increased significantly after PPI treatment in both *H. pylori*-negative and *H. pylori*-positive patients.[71] Tseng et al. conducted a 2-year follow-up study on 6 early-stage cancer patients in Taiwan to characterize the effects of subtotal gastrectomy on the gastric microbiome. *Streptococcus* sp and *Prevotella* were the two most abundant genera after surgical treatment of gastric cancer and predicted gene functions from 16S rRNA gene sequencing showed a shift from *N*-nitrosation genes prior to surgery to bile salt hydrolase, NO, and N_2O reductase, which reflect the altered gastric environment after the surgery.[72] Further studies to determine the clinical implications of elevated numbers of *Streptococcus* sp. in the stomach in health and disease are necessary.

Numerous observations suggest that chronic microbial colonization can impact the immune control of other unrelated pathogens. Possible interactions between *Mycobacterium tuberculosis* infection and Helicobacter persistence have been investigated in mice. Compared with Helicobacter-free mice, *M. tuberculosis* infection of *H. hepaticus*-infected mice triggers a modification of the gut microbiota, a stimulation of innate immunity, hypercytokinemia, accumulation of activated T cells, senescent cells, which results in severe lung tissue injury.[73] These findings suggest that the impact of prior Helicobacter colonization and subsequent *M. tuberculosis* parasitism might be greater than previously thought. In a mouse model for chronic psychosocial stress, which promotes a microbial signature of gut inflammation (characterized by expansion of Proteobacteria, specifically *Helicobacter* sp.), the presence or absence of exposure to *Helicobacter* sp. during the experiment contributed to the variability of results between laboratories.[74] Ffar2, a receptor for short-chain fatty acids, metabolites of dietary fiber fermentation by gut microbiota, is essential for the elimination of *H. hepaticus* from gut microbiota and for the suppression of colonic inflammation and carcinogenesis.[75]

Probiotics are living microorganisms which have health benefits on the host when administered in adequate amounts.[76] Nakae et al., in a study on 44 healthy controls and 44 functional dyspepsia (FD) patients in Japan, found that significant dysbiosis with a reduced abundance of *Prevotella* sp. in their gastric juice was associated with FD. A significant inverse correlation was reported between an abundance of *Prevotella* sp. and severity of postprandial distress-like syndromes and treatment of FD patients with a yogurt containing a probiotic strain of *Lactobacillus gasseri* daily for a 12-week period reversed the dysbiosis and relieved their symptoms.[77] The administration of probiotics for correction of gastric dysbiosis may be a rational and promising direction for the treatment of FD. However, the microbiota of gastric aspirates is distinct from that in mucosal biopsies and does not provide a reliable representation of the mucosal-associated bacteria.[63] In addition, the evaluation of symptoms of FD by Nakae et al. was questionnaire-based; hence, this might be subjective and cannot entirely rule out a placebo effect.

In another study, *Helicobacteraceae* decreased with a probiotic cocktail (*Lactobacillus acidophilus*, *Bifidobacteria bifidum*, and *Bifidobacteria infantum*) in a rat model of colon cancer. This probiotic treatment altered the gut microbiota by promoting the growth of Lactobacilli to the detriment of other bacteria and reduced cancer via TLR2 signaling.[78] Prebiotic feeding (galacto-oligosaccharides) resulted in a decreased abundance of Helicobacters in wild-type 129 mice.[79] C57BL/6J mice with high fat diet had a dysbiosis characterized by a dramatic increase of bacteria belonging to the *Helicobacter* genus. Treatment with quercetin reversed this effect, suggesting a prebiotic capacity.[80] Sodium butyrate treatments mitigated in vitro ammonia generation and decreased the relative abundance of *Helicobacter* sp. in the cecal contents of laying hens.[81] *Helicobacter* sp was found to be decreased in the presence of laminarin or sodium alginate in a rat model[82] and taurine reduced the abundance of Proteobacteria, especially Helicobacters in BALB/c mice.[83]

DISCLOSURES OF INTERESTS

The authors declare no conflict of interest.

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