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Contents

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EDITORIAL

ORIGINAL ARTICLE

Retrospective Study

Observational Study

Basic Study

LETTER TO THE EDITOR

ABOUT COVER

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LETTER TO THE EDITOR

Role of gut microbiota and *Helicobacter pylori* in inflammatory bowel disease through immune-mediated synergistic actions

Zhi-Hao Deng, Xin Li, Li Liu, Hai-Min Zeng, Bo-Fan Chen, Jie Peng

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Zhi-Hao Deng, Li Liu, Hai-Min Zeng, Bo-Fan Chen, Jie Peng, The Second Clinical Medical College, The Second Affiliated Hospital, Jiangxi Medical College, Nanchang University, Nanchang 330006, Jiangxi Province, China

Xin Li, The First Clinical Medical College, The First Affiliated Hospital, Jiangxi Medical College, Nanchang University, Nanchang 310006, Jiangxi Province, China

Co-first authors: Zhi-Hao Deng and Xin Li.

Corresponding author: Jie Peng, MD, Doctor, The Second Clinical Medical College, The Second Affiliated Hospital, Jiangxi Medical College, Nanchang University, No. 1 Minde Road, Donghu District, Nanchang 330006, Jiangxi Province, China. jie_peng@email.ncu.edu.cn

Abstract

A recent study published in the *World Journal of Gastroenterology*, suggests that transplanting the gut microbiota from healthy donors can alleviate the pathological processes linked to inflammatory bowel disease (IBD), particularly Crohn's disease. In addition, that paper illustrates the effect of changes in the gut microbiota on IBD and points out that altered mesenteric adipose tissue caused by the gut microbiota and creeping fat lead to increased inflammation, which exacerbates IBD. Moreover, recent research has shown that the interaction between *Helicobacter pylori* (*H. pylori*) and the gut microbiota is mediated through immune mechanisms, resulting in a synergistic impact on IBD. Therefore, in this manuscript, we will focus on the role of the gut microbiota and *H. pylori* in the immune response to IBD, as well as the possible impact of *H. pylori* on the gut microbiota. We will also explore their individual and synergistic immune effects on IBD and look at future therapeutic perspectives for IBD.

Key Words: Gut microbiota; *Helicobacter pylori*; Inflammatory bowel disease; Inflammation regulation; Interactions between microorganisms; Immune modulation

Core Tip: The gut microbiota and *Helicobacter pylori* (*H. pylori*) are crucial in maintaining immune balance. *H. pylori* may protect against inflammatory bowel disease (IBD) by regulating the immune system and suppressing excessive inflammation. It also influences the gut microbiota, potentially modulating IBD by adjusting microbiota abundance and through immune-mediated synergistic effects. However, the relationship between *H. pylori* and the gut microbiota needs further investigation. Understanding these interactions could inform the development of new IBD treatments and therapeutic strategies.

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TO THE EDITOR

Comprising Crohn's disease (CD) and ulcerative colitis (UC), inflammatory bowel disease (IBD) is a worldwide chronic inflammatory disease of the gastrointestinal tract[1]. In recent years, the global incidence of IBD has steadily increased[2]. IBD has a profound impact on the quality of life of patients, with long-term physical symptoms leading to reduced physical and nutritional status and recurrent episodes of the disease exacerbating psychological stress, which makes many patients suffer from associated anxiety and depression. Moreover, frequent medical interventions for IBD significantly impair quality of life, restricting social and work activities[3]. While the specific cause of IBD remains unclear, its pathology is believed to result from a combination of genetic, environmental, immune, and gut microbiota factors.

The gut microbiota plays a crucial role in maintaining gastrointestinal balance and immune system function. They regulate the immune response through complex metabolic activities and direct interactions with immune cells, ensuring normal gut function and defense mechanisms[4]. Wu *et al*[5] studied the alteration of the gut microbiota in patients with CD and observed that the abundance of the gut microbiota was lower in individuals with CD than in those without. They especially noted that the suppressed gut microbiota in CD patients may exacerbate intestinal inflammation and fibrosis and that modification of the gut microbiota by faecal microbiota transplantation (FMT) may alleviate CD. They not only noted the effect of the gut microbiota on inflammation but also suggested that altering the gut microbiota by FMT could have a therapeutic effect on IBD. While Wu *et al*[5] focused on the beneficial effects of restoring microbial homeostasis in patients with IBD, *Helicobacter pylori* (*H. pylori*), a well-known gastric pathogen, may increase the complexity of this relationship.

H. pylori, a common gastric pathogen, is typically associated with conditions such as gastritis, gastric ulcers, and gastric cancer. However, emerging research suggests that *H. pylori* may also significantly influence the development of IBD through complex interactions with the gut microbiota and the immune system[6-8]. *H. pylori* influences immune mechanisms and alters the composition of the gut microbiota, thus impacting the immune response by regulating inflammation and immune evasion mechanisms[9]. Therefore, understanding how the gut microbiota and *H. pylori* interact within the immune system is crucial for uncovering the pathological mechanisms of IBD.

This paper explores the role of the gut microbiota and *H. pylori* in the development of IBD, highlighting immune-mediated synergies and exploring potential therapeutic strategies derived from these mechanisms.

RELATIONSHIP BETWEEN GUT MICROBIOTA AND IBD

The gut microbiota plays a significant role in the pathogenesis of IBD. The gut microbiota of patients with IBD often shows dysbiosis, including a decrease in microbial diversity and an increase in harmful bacteria. The gut microbiota also plays a significant role in regulating intestinal immunity, which can worsen the pathogenesis of IBD by altering the balance between inflammatory cytokines and anti-inflammatory mechanisms. Moreover, the microbiota is also closely related to intestinal barrier function, affecting the integrity of the intestinal barrier and playing an important role in IBD processes. Wu *et al*[5] reported that significant changes in the gut microbiota in CD patients were associated with increased expression of pro-inflammatory factors due to mesenteric adipose tissue with inflammatory and fibrotic features and creeping fat, as revealed by transplantation of the gut microbiota from CD patients into a mouse model. These authors noted that alterations in the gut microbiota are considered a key factor in the pathogenesis of CD and that they may influence the inflammatory response through multiple mechanisms, comprising modulating the activity of immune cells and stimulating the production of inflammatory factors. Hundreds of bacterial lineages associated with IBD were identified by analysing faecal metagenomes from thousands of IBD patients and healthy controls in a study conducted by Kumbhari *et al*[10]. This study revealed genetic variations in these bacteria related to inflammation, including responses to oxidative stress, nutrient synthesis, and immune evasion. This study also revealed that the loss of certain beneficial bacterial lineages can predict the severity of inflammation. Additionally, research indicates that IBD patients often display dysregulation of the gut microbiota, which is marked by decreased microbial diversity and an increase in harmful bacteria. For example, the proportion of anaerobic bacteria beneficial for IBD, such as *Clostridia*, is

decreased in the gut of IBD patients, whereas the proportion of opportunistic bacteria, such as *Enterobacteria*, is significantly increased[11,12]. Furthermore, some opportunistic pathogens, such as adherent-invasive *Escherichia coli* (*E. coli*) and toxigenic *Bacteroides fragilis* (*B. fragilis*), promote inflammation in IBD patients by producing inflammatory mediators such as adhesin and *B. fragilis* toxin[10]. This leads to the breakdown of the intestinal mucosa and the disruption of tight junctions between intestinal epithelial cells. These changes increase intestinal permeability, leading to further inflammation and damage to the intestinal wall.

RELATIONSHIP BETWEEN *H. PYLORI* AND IBD

Although the main site of *H. pylori* infection is the stomach, the onset of IBD is related to innate and adaptive immunity, so the effect of *H. pylori* on immunity is a factor leading to the onset of IBD. Many studies have demonstrated that *H. pylori* may have a protective effect against IBD[13,14], although this remains a topic of debate among researchers. Piovani *et al*[15] conducted an umbrella review to analyse the relationship between *H. pylori* and IBD and found an association between *H. pylori* and a lower incidence of IBD (risk ratio = 0.38; 95% confidence interval: 0.31–0.47). However, they did not investigate the underlying mechanisms and proposed that this association might not be directly due to *H. pylori* reducing IBD incidence but could involve other shared environmental or genetic factors. For example, regions with higher *H. pylori* infection rates often have lower IBD rates, suggesting that geographic and environmental factors might confound the true causative relationship.

H. pylori is thought to reduce inflammation through several mechanisms. The cytotoxin-associated antigen A (*CagA*) gene in *H. pylori* may aid in achieving remission in IBD patients[13]. This remission could occur through modulation of the Th17/regulatory T (Treg) cell immune response by increasing interleukin (IL)-10 and IL-13 levels, promoting the conversion of macrophages to an anti-inflammatory M2 phenotype, and inhibiting the Toll-like receptor signaling pathway (Figure 1)[16]. Additionally, infection with a CagA-positive *H. pylori* strain increased the number of CD163+ and CD163+/IL-10+ monocytes associated with the anti-inflammatory response. Furthermore, *H. pylori* enhances the expression of IL-1β and IL-18 by activating the NOD-like receptor thermal protein domain associated protein 3 inflammasome, which is crucial in the immune regulation of IBD. This activation can reduce intestinal inflammation and improve IBD prognosis by inhibiting the Th17 response and promoting Treg cell function. Studies have also shown that *H. pylori* neutrophil-activating protein, a virulence factor in *H. pylori* similar to CagA, can promote a Th1 immune response by inducing the activation of neutrophils and monocytes, which may have a protective effect against Th2-based diseases such as UC[17]. Other components of *H. pylori*, such as flagella and superoxide dismutase[18], may also promote immune evasion by inhibiting the production of proinflammatory cytokines or affecting the immune response. Furthermore, although antibiotics reduced the infection rate of *H. pylori* in patients with IBD, those without a history of antibiotic use still present significantly lower *H. pylori* infection rates than healthy controls[19]. Thus, multicentre prospective cohort studies are urgently needed to confirm *H. pylori* infection status and treatment history immediately following an IBD diagnosis. Confounding factors in these studies should be better controlled to draw definitive conclusions, and additional experiments are needed to clarify how *H. pylori* reduces the incidence of IBD through immune pathways.

In addition to its impact on IBD through immune mechanisms, *H. pylori* may influence the gut microbiota, thereby affecting IBD. However, the complex relationship between *H. pylori* presence or eradication and how subsequent shifts in the gut microbiota impact IBD development remain underexplored. Heimesaat *et al*[20] demonstrated that chronic infection with *H. pylori* leads to significant alterations in the microbiota of the stomach and large intestine in Mongolian gerbils, especially in the uninflamed distal gastrointestinal tract. This study revealed notable increases in *E. coli*, *Enterococcus*, and *Bacteroides*/*Prevotella* in the caecum and colon. Additionally, *Akkermansia*, a bacterium that degrades mucus and is linked to gut health and protective effects against IBD, was detected exclusively in *H. pylori*-infected gerbils. Notably, *H. pylori* eradication has been found to adversely affect the gut microbiota, especially with treatment regimens containing antibiotics, such as triple therapy or quadruple therapy with bismuth[21,22]. Jakobsson *et al*[23] demonstrated that the diversity of the gut microbiota was significantly lower after eradication than before, and found that the proportion of *Actinobacteria* was significantly lower. This may be due to the adverse effects of antibiotics on the gut microbiota. There are currently two possible mechanisms by which *H. pylori* affects the gut microbiota. The first is that the acidic environment in the stomach was altered by chronic *H. pylori* infection, allowing more microbiota to pass through the gastric acid barrier to reach the distal gut[24]. The second is that reduced leptin and growth hormone-releasing peptide secretion in *H. pylori*-infected individuals could indirectly affect the abundance of the gut microbiota by modulating gastric acid secretion and immune responses[25,26]. Through these mechanisms, *H. pylori* can increase the abundance of the gut microbiota. However, *H. pylori* infection also leads to an increase in harmful bacteria that can worsen IBD, including *Proteobacteria* and *Actinobacteria*[27,28]. Therefore, the mechanism by which *H. pylori* indirectly influences IBD development through its impact on the gut microbiota requires further investigation.

INTERACTION BETWEEN GUT MICROBIOTA AND *H. PYLORI* IN THE IMMUNE SYSTEM

The composition and abundance of the gut microbiota significantly impact the development of IBD by helping to maintain the intestinal balance through immune system regulation. Typically, in the gut microbiota, probiotics such as *Clostridium* species synthesize short-chain fatty acids (SCFAs). These fatty acids are essential for promoting the growth of Treg cells, reducing inflammatory processes, and strengthening the gut barrier[29]. However, when the gut microbiota is

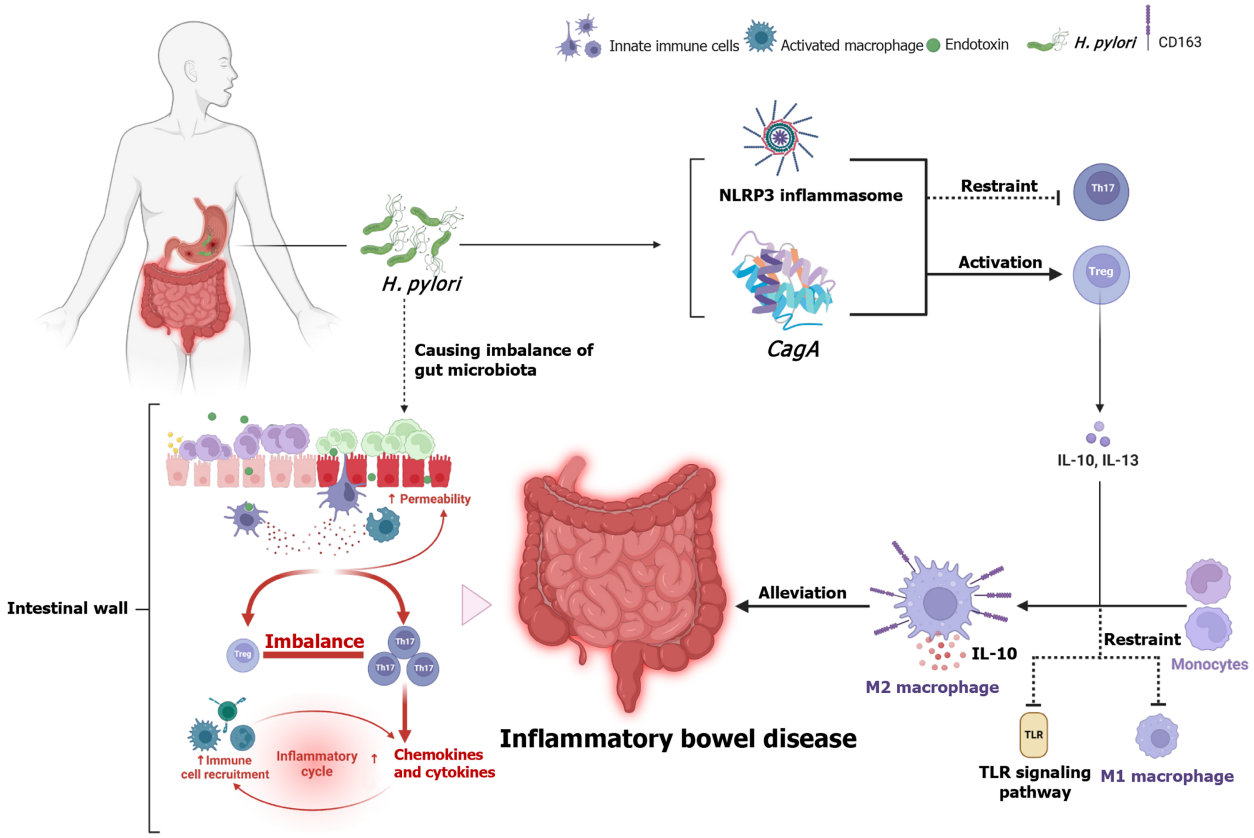

Figure 1 Potential immune mechanisms of *Helicobacter pylori* on inflammatory bowel disease exacerbation and alleviation. The cytotoxin-associated antigen A gene and NOD-like receptor thermal protein domain associated protein 3 inflammasome activate the Th17/regulatory T (Treg) cell response, stimulating Treg cell, interleukin (IL)-13, and IL-10 expression. IL-13 and IL-10 synergistically promote the macrophage shift to the M2 phenotype and inhibit the M1 phenotype. M2-type macrophages inhibit Toll-like receptor signaling, stimulating CD163 production, and release anti-inflammatory IL-10. However, *Helicobacter pylori* could increase inflammatory flora, produce endotoxins, modulate the Th17/Treg cell response, contribute to the release of Th17 factors, recruit immune cells, exacerbate inflammation, and worsen inflammatory bowel disease. *CagA*: Cytotoxin-associated antigen A; *H. pylori*: *Helicobacter pylori*; IL: Interleukin; NLRP3: NOD-like receptor thermal protein domain associated protein 3; Treg: Regulatory T; TLR: Toll-like receptor.

out of balance, the immune system becomes overactive, resulting in uncontrolled inflammation and triggering intestinal diseases. For example, segmented filamentous bacteria induce Th17 cells, which promote IBD by producing chemokines and cytokines[30]. Variations in host genes, such as *Atg16 L1* and *NOD*2, which are linked to IBD, may intensify inflammatory responses by impacting the capacity of the microbiome to regulate immunity[31,32].

H. pylori infection has complex immunomodulatory effects on IBD; it can reduce inflammation by modulating innate immune pathways and alleviate disease symptoms by influencing adaptive immune responses[16]. Additionally, the immunological interactions between the gut microbiota and *H. pylori* may influence IBD progression. Together, these factors can affect the severity of IBD by modulating the balance between Treg and Th17 cells. When bacterial genera that cause IBD, such as *Mycobacterium spp*[33], are overabundant in the gut, Th17 cell activity can be increased, and the inhibitory effect of Treg cells can be suppressed[34]. When this effect is stronger than that of *H. pylori* in suppressing Th17 cell activity and promoting Treg cell function, it may exacerbate IBD (Figure 1)[35]. In conclusion, the gut microbiota and *H. pylori* jointly influence the course of IBD through a complex immunomodulatory mechanism, forming a microbial-immune-IBD interaction axis. Notably, this mechanism requires further study.

TREATMENT PROSPECTS FOR IBD

Current IBD treatment strategies encompass various approaches, including microbiome regulation and immune regulation, which target different mechanisms to control inflammatory responses and enhance patient outcomes. With respect to the regulation of the gut microbiota, a retrospective study of 200 patients with IBD conducted by Dore *et al*[36], reported that probiotics reduced the incidence of many adverse events. Probiotics improve IBD through various mechanisms depending on the strain. *Lactobacillus*, for example, inhibits pathogenic bacteria by generating antimicrobial substances such as lactic acid, hydrogen peroxide, and bacteriocin. It also modulates T-cell subsets, reduces proinflammatory cytokine production, and enhances the anti-inflammatory response. *Bifidobacterium* enhances intestinal barrier function by stimulating the expression of tight junction proteins, lowering the intestinal potential of hydrogen, and promoting intestinal epithelial repair by fermenting carbohydrates to produce SCFAs such as butyric acid. The VSL3 probiotic combination further reduces intestinal inflammation by restoring microbiota balance, increasing beneficial

bacteria, and improving gut barrier function and the immune response. Through synergies, these strains offer multiple potential therapeutic benefits for the management of IBD[37-39]. However, in certain cases, probiotic supplementation may lead to bacteraemia or intestinal damage, potentially due to the high proportion of specific bacteria in the probiotics, necessitating further research to ensure safety[40]. Owing to limited trials, some consensuses were reached at the first International Rome Consensus Conference on FMT for IBD, acknowledging that FMT can effectively alleviate some cases of IBD. However, in routine clinical practice, there is insufficient evidence to recommend FMT as a treatment for IBD, and its use is generally limited to research settings. Therefore, further research is needed to identify FMT therapies for IBD [41].

Combining immunotherapies with the gut microbiota and *H. pylori* regulation offers significant potential for treating IBD. Biologics have been widely used to treat IBD by suppressing the production of proinflammatory factors such as tumour necrosis factor-alpha, whereas immune checkpoint inhibitors promote anti-inflammatory responses by increasing T-cell activity. However, these therapies may trigger an increase in intestinal inflammation, so caution is needed during treatment. Certain bacteria, such as *Faecalibacterium prausnitzii,* can help reduce inflammation by regulating the balance of Th17 and Treg cells[42]. *H. pylori* contributes to immune regulation in IBD by inhibiting Th17 cells and promoting Treg cells. By regulating the gut microbiota and *H. pylori* infection, combined with immunotherapy, a more personalized treatment regimen can be developed to reduce perturbation of the gut microbiota and decrease the side effects of biologics and immune checkpoint inhibitors[43]. Future studies should focus on exploring how best to combine these treatments to improve the therapeutic efficacy of IBD and the specific regulatory mechanisms of *H. pylori* and the gut microbiota in IBD immunotherapy. This combination therapy is expected to provide a more effective and personalized treatment strategy for IBD patients.

PROSPECTS FOR FUTURE RESEARCH

Future research should focus on further exploring the complex relationships among *H. pylori*, the gut microbiota, and IBD, particularly their specific roles in immune regulation. First, a deeper investigation is needed to understand how *H. pylori* impacts the gut microbiome under various host conditions. More work is also needed to understand the dual role of *H. pylori* in IBD patients both as a potential protective factor and as a possible inducer of gastric diseases. Findings should be confirmed through detailed mechanistic studies and large-scale clinical trials. Second, it is essential to design and validate individualized treatment regimens targeting *H. pylori* to ensure that the overall balance of the gut microbiota is maintained without causing gastric diseases. Finally, innovative treatment strategies are needed to avoid the potential adverse effects of *H. pylori* while effectively enhancing outcomes for IBD patients. These studies will provide a crucial foundation for the development of more precise treatment strategies.

CONCLUSION

Overall, the gut microbiota and *H. pylori* are important in maintaining immune homeostasis, and *H. pylori* possibly plays a protective role in IBD by regulating the immune system through various ways, such as regulating T cell activation, secreting immune regulatory factors, protecting the intestinal barrier, and inhibiting excessive inflammatory response. *H. pylori* also has a regulatory effect on the gut microbiota and can regulate IBD by regulating the abundance of gut microbiota and through immune-mediated synergies. However, some studies have shown that *H. pylori* may increase the abundance of gut microbes harmful to IBD, so more studies are still needed to verify the effect of *H. pylori* on the gut microbiota in IBD. Current IBD treatments involve microbiome regulation and immunotherapies, including FMT and probiotics. Future research should explore the optimal combinations of these treatments, validate their efficacy and safety through large-scale clinical trials, and develop precise treatment strategies using emerging technologies.

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ORCID number: Zhi-Hao Deng 0009-0007-6239-8324; Xin Li 0009-0008-4176-1128; Li Liu 0009-0002-6877-278X; Hai-Min Zeng 0000-0002-8065-8712; Bo-Fan Chen 0009-0001-5711-6181; Jie Peng 0000-0003-4040-0327.

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