Helicobacter pylori may participate in the development of inflammatory bowel disease by modulating the intestinal microbiota

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Abstract

Inflammatory bowel disease (IBD) is a non-specific inflammatory disease of the gastrointestinal (GI) tract that is generally accepted to be closely related to intestinal dysbiosis in the host. GI infections contribute a key role in the pathogenesis of IBD; however, although the results of recent clinical studies have revealed an inverse correlation between Helicobacter pylori (*H. pylori*) infection and IBD, the exact mechanism underlying the development of IBD remains unclear. *H. pylori*, as a star microorganism, has been a focus for decades, and recent preclinical and real-world studies have demonstrated that *H. pylori* not only affects the changes in the gastric microbiota and microenvironment but also influences the intestinal microbiota, indicating a potential correlation with IBD. Detailed analysis revealed that *H. pylori* infection increased the diversity of the intestinal microbiota, reduced the abundance of Bacteroidetes, augmented the abundance of *Firmicutes*, and produced short-chain fatty acid-producing bacteria such as *Akkermansia*. All these factors may decrease vulnerability to IBD. Further studies investigating the *H. pylori*-intestinal microbiota metabolite axis should be performed to understand the mechanism underlying the development of IBD.

Keywords: *Helicobacter pylori*; Inflammatory bowel disease; Intestinal microbiota

Introduction

Inflammatory bowel disease (IBD) consists of Crohn's disease (CD) and ulcerative colitis (UC), and it is a group of complex diseases that have a protracted course characterized by periodical remissions and relapses; in addition, IBD significantly impacts the quality of life and working competence. During the past two decades, our understanding of the pathogenesis of this complex disease has improved significantly. Infection and immune response are generally considered to play a crucial role in the pathogenesis of IBD; however, results of recent studies indicate that not all infections or microbial exposures exert the same effect on the development of IBD. *Helicobacter pylori* (*H. pylori*), which is well known to lead to chronic atrophic gastritis, peptic ulcers, and gastric cancer, showed an inverse correlation with IBD in several studies with a large sample size, especially a significant negative relationship with CD rather than UC.[1,2] To date, several hypotheses have been proposed for this inverse correlation, including a negative socioeconomic distribution between harboring *H. pylori* infection and IBD and the counter-effect of *H. pylori* infection on the immune system.[3] However, the exact mechanism underlying this phenomenon remains unclear. In this review, we provide an overview of the studies performed thus far on the intestinal microbiota and IBD and the effect of *H. pylori* on the intestinal microbiota and IBD as a friend or a foe in the pathogenesis of IBD, which highlights the possible benefit of the presence of *H. pylori* in humans.

IBD and Intestinal Microbiota: Friend or Foe

The human "microbiota" is defined as an entire ecosystem consisting of bacteria, viruses, fungi, and bacteriophages which cooperatively acts as an entity within the human. The microbiome of a healthy adult has 10^{13}–10^{14} bacterial cells and an estimated 1000 kinds of various bacterial species; however, the unique population of fecal microbiota in each individual is fairly constant over time, and the fluctuations of these microorganisms' numbers are considered as a response to developmental or environmental factors, with the most prominent factors being diet and exposure to antibiotics. In the colon of a healthy

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adult, the most abundant bacterial phyla resided are *Bacteroidetes* and *Firmicutes*.[4] Other important groups of microorganisms occurring at a lower frequency include *Proteobacteria, Actinobacteria, Fusobacteria,* and *Verru- comicrobia*.[5] The host immune system influences the intestinal microbial communities. In addition, alterations in the microbial community, in turn, modulate the outcomes of the intestinal inflammatory disease.[6]

The pivotal mechanism for the development of IBD appears to involve a deregulated immune response to the commensal flora in an individual with genetic susceptibility. Several studies indicate that the disordered intestinal microbiome is the underlying pathogenesis for IBD, and the imbalance between "beneficial" and "harmful" bacteria is defined as "dysbiosis."[7] To our knowledge, at least two dominant patterns of alterations in the intestinal microbiota are generally accepted as distinguishing features in patients with IBD. Compared with healthy individuals, patients with IBD show a decrease in the overall diversity and abundance of intestinal microbiota. Meanwhile, mucosal biopsies of patients with IBD reveal a decrease in the abundance of *Firmicutes* and *Bacteroidetes* and an increase in the abundance of *Proteobacteria* and *Actinobacteria*, which are generally considered the "foes" of IBD.[8] Furthermore, patients with IBD may have a significant reduction of the bacteria number, which may be important in conferring protection from intestinal inflammation. For instance, patients with IBD have decreased levels of short-chain fatty acids (SCFAs) in the stool, indicating the potential role of *Ruminococcaceae,* which is an important butyrate producer and the key "friend" of IBD.[9]

Recent studies have shown that surprisingly, *H. pylori* has the potential beneficial effects as a friend in asthma, rheumatoid arthritis, and IBD. These novel results change our knowledge regarding *H. pylori*, which is typically a harmful bacterium that leads to the development of multiple gastric diseases.[10] Epidemiological evidence and the interaction of *H. pylori* with other microbiota should be studied to precisely understand the role of *H. pylori*.

Global Epidemiological Trends of IBD and *H. pylori* with the Interesting Inverse Correlation

Significant geographic and temporal trends in the incidence of IBD have been reported in several population-based cohort studies.[2] The results revealed that the incidence of IBD, regardless of CD or UC, appears to be increasing in some areas and vary based on geographic location.[11,12] Interestingly, the incidence and prevalence of IBD are at a low level in Asia, which is an area with a high abundance of *H. pylori;* furthermore, some newly industrialized regions in eastern Asia have shown an increase in the incidence of IBD (for instance, the annual percentage changes in the incidence of CD and UC in Taiwan, China, were +4.0% and +4.8%, respectively),[12] and the prevalence of *H. pylori* infection has presented a decreasing trend (eg, in Hangzhou, China, the prevalence of *H. pylori* infection in juvenile individuals decreased from 21.6% to 17.2% between 2007 and 2014).[13]

Unlike the pathogens that cause classic infective gastroenteritis, such as *Salmonella* and *Campylobacter*, *H. pylori* is a spiral-shaped and Gram-negative bacterium identified in the human gastric mucosa by Marshall and Warren in 1984,[14] and is well known to lead to chronic atrophic gastritis, peptic ulcers, gastric cancer, and mucosa- associated lymphoid tissue lymphoma.[15] *H. pylori* is the most popular bacterial pathogen in humans and is present in the upper gastrointestinal (GI) tract of >50% of the whole population among individuals of all ages.[16] *H. pylori* infection showed a predilection for the young population in developing countries than in industrialized regions, and the incidence of *H. pylori* infection has decreased in industrialized countries in recent years,[17] which demonstrates an interesting inverse geographic and temporal trend for IBD. The risk of *H. pylori* infection is proven to be related to poor living conditions and socioeconomic status early in life.[18] Infective gastroenteritis in the first year of life was listed as a risk factor for IBD[19]; however, several studies have demonstrated a negative correlation between *H. pylori* seropositivity and the development of IBD regardless of age, ethnicity, *H. pylori* test techniques, and IBD subtype.[20-22] Furthermore, patients with IBD have a significantly increased prevalence of *H. pylori*-negative gastritis.[3] Some studies have reported that *H. pylori* is a GI infection distinct from other infections.[23] The negative association between *H. pylori* infection and IBD was observed both *in vivo* and *in vitro*. *H. pylori* deoxyribonucleic acid (DNA) suppressed the release of pro- inflammatory cytokines by dendritic cells and attenuated the severity of colitis in a mouse model of IBD.[24] A recent preclinical study on serum exosomes derived from *H. pylori*-positive gastritis patients showed a potential explanatory pathway for the inverse phenomenon.[25] Other animal studies suggested regulatory T (Treg) cells,[26] T-helper (Th17) cells,[26] regulatory B (Breg) cells,[27] and M2 macrophages[28] might make a positive effect on the protective function of *H. pylori* infection for colitis. In addition, the luminal delivery of *H. pylori* genomic DNA ameliorates the severity of chronic experimental colitis.[29] Several explanatory hypotheses have been proposed for this meaningful phenomenon, including an inverse socioeconomic distribution between harboring *H. pylori* and IBD and the counter-effect of *H. pylori* on the immune system; however, the key mechanism underlying the development of IBD remains unclear.[20,30] The alteration in microbiota induced by *H. pylori* infection has emerged as a potential explanation.

H. pylori Infection and the Alteration in the Intestinal Microbiota

Despite the varying results obtained in different studies, the focus of most recent studies has been the difference in gastric microbiota between patients with and without *H. pylori* infection.[15,31] Hypochlorhydria and hypergastrinemia induced by *H. pylori* may change the intestinal microbiota. Analysis of the relative abundance of different bacteria along the entire GI tract of a Mongolian gerbil model showed an altered composition of the intestinal microbiota after chronic infection (14 months)

with *H. pylori*. The results revealed differences in microbiota in the distal but not in the proximal portion of the inflamed GI tract. Further molecular analyses revealed that *Akkermansia,* an important member of healthy species in the intestinal mucosa,[32,33] was exclusively abundant in the large intestine.[34] Another *H. pylori*-related experiment performed using the C57BL/6 mouse model of *H. pylori* infection focused on the local and distant microbial community structures and relative microbial abundance. The results of the study revealed that *H. pylori* influenced the microbial population structure of the distal intestine over time. Furthermore, the results of multiple temporal analyses revealed a persistently altered abundance of the intestinal microbiota (1, 3, and 6 months)[35].

A few studies have been performed on the intestinal microbiota in humans infected with *H. pylori*. A study with a small sample size, including 18 Japanese children and adults from five families with or without *H. pylori* infection, aimed to investigate the potential influence of *H. pylori* infection on the intestinal microbiota. The results revealed no significant difference in the intestinal microbiome between the *H. pylori*-positive and *H. pylori*-negative groups.[36] However, the limitations of this study included a small sample size, different age groups, and participants with a kinship relation. The results of a recent study including 47 participants from a region in China with a high prevalence of *H. pylori* infection showed that the species and Shannon index were higher in participants with past or current *H. pylori* infection than in those without *H. pylori* infection. A significant decrease was observed in the abundance of *Bacteroidetes* in patients with past or current *H. pylori* infection, and the average relative abundance of *Firmicutes* showed an increasing trend in the group with previous *H. pylori* infection compared with the *H. pylori*-negative group.[37] Although the exact mechanism underlying the relationship between *H. pylori* infection and changes in the intestinal microbiota has not been established thus far, an interplay with an intact type IV secretion system is thought to induce distinct shifts in the composition of the gut microbiota.[38] Furthermore, *H. pylori*-induced hypochlorhydria and hypergastrinemia in the upper GI have been hypothesized as factors underlying the changes in the microbiota of the large intestine.[34]

Multiple antibiotic regimens have been evaluated for the treatment of *H. pylori* infection, and a 14-day bismuth-containing quadruple therapy has been proposed as the first-line standard regimen.[39] However, the *H. pylori* eradication treatment produced a significant change in the human intestinal microbiome and decreased bacterial diversity,[40,41] for example, the eradication treatment caused a dramatic decline in *Actinobacteria*. Some patients continued to have an altered intestinal microbiota even 4 years after the eradication treatment.[42] These results were consistent with those reported in a randomized clinical trial in Chinese adults with or without *H. pylori* infection. To explore the significance of the intestinal microbiota, a study investigating the addition of *Clostridium butyricum* as a probiotic to the standard quadruple anti-*H. pylori* therapy is underway. Patients receiving the eradication therapy with the probiotic showed improved GI symptoms and an increased *Bacteroidetes/Firmicutes* ratio.[43] Moreover, it is important to identify whether alterations in the intestinal microbiota affect real-world outcomes. Data from a health insurance database from Taiwan, China, showed that treatment for *H. pylori* infection accounted for a significantly elevated risk of autoimmune diseases or IBD (hazard ratio, 2.36; 95% confidence interval, 2.14–2.59).[44]

To conclude, *H. pylori* infection not only induces changes in the gastric microenvironment but also interacts with microbiota in the large intestine, creating a new physiological balance in the GI tract. Although limited data are available regarding the changes in the intestinal microbiota in humans and animals,[45-47] the results avilable thus far demonstrate an "IBD-protective" profile of the intestinal microbiome, such as an increase in alpha- and beta- diversity,[48] *Firmicutes* phyla,[35] and *Akkermansia* species.[34] Therefore, we speculate that alterations in the intestinal microbiota induced by *H. pylori* and eradication contribute to the pathogenesis of IBD.

Alterations in the Immune Response Induced by *H. pylori* Affect the Development of IBD

Changes in immune response instead of changes in the intestinal microbiota are more recognized effects of *H. pylori* infection. Several hypotheses have been proposed to elucidate the relationship between *H. pylori* and IBD; however, the exact relationship between *H. pylori* infection and IBD remains unclear. One of the theories suggests that *H. pylori* infection-associated diseases are driven by the expression of Th1 and Th17 cytokines secreted by pathogenic T cells; however, a majority of individuals without symptoms receive protection from Treg-predominant response to *H. pylori* infection by suppressing the Th1, Th17, and Th2 responses not only in the gastric mucosa but also in the rest of the GI tract. *H. pylori*-induced Tregs play an important role in alleviating the symptoms of colitis in models of IBD; in addition, other immune factors are involved in resolving these symptoms. Previous studies demonstrated that *H. pylori* infection alleviated acute and chronic colitis induced by dextran sulfate sodium (DSS), and Breg cells played a critical role in this process. The levels of $CD19^+$ interleukin 10 $(IL\text{-}10)^+$ Breg cells in different tissues were higher in the *H. pylori*/DSS-cotreated groups than in the DSS-treated groups.[27] Moreover, Breg cells attenuate the mucosal inflammatory responses in the gut.[49] They cooperate with dendritic cells to promote differentiation of Treg cells, leading to the inhibition of effective T cell responses. However, the results of several clinical analyses did not show a difference between symptomatic and asymptomatic patients with *H. pylori* infection in correlation with IBD, which indicated that the classical theory may not be sufficient to explain the relationship between *H. pylori* infection and IBD.

Some protective associations may not be directly driven by *H. pylori*. *H. pylori* infection modifies the composition of the gut microbiota. However, the impact of *H. pylori* on gut microbiota-derived metabolites remains unknown.

Gut microbiota-derived metabolites such as SCFAs and bile acid metabolites are the key factors in the development of IBD.[50] SCFAs have diverse effects on mucosal immunity, including the expansion of Treg cells,[51] antiproliferative effects via histone deacetylase inhibition,[52] and the maintenance of epithelial homeostasis through the production of IL-18 via inflammasome activation.[53] The eradication of *H. pylori* disturbs the balance in intestinal microbiota, mimicking the components of the microbiota in IBD.[4,54,55] Reduced microbial diversity and SCFA- producing bacteria (such as *Ruminococcaceae)* and a potential increase in pathogenic bacteria may lead to a decrease in the energy source in epithelial cells, alteration in the differentiation of Treg cells, degradation of mucus, induction of mucosal inflammation, and a change in mucosal permeability. Further studies should aim to identify the metabolite profile of patients with *H. pylori* infection with or without IBD, and the detailed mechanism underlying the *H. pylori*-gut microbiota–metabolism axis should be explained.

Summary

The cumulative evidence from preclinical and real-world studies showed a possible negative association between *H. pylori* infection and IBD. The changes in intestinal microbiota induced by *H. pylori* infection have the potential to protect against IBD; thus, selective eradication and surveillance of patient subgroups with a high risk of *H. pylori*-related sequelae (eg, gastric ulcer and cancer) would be more appropriate than the indiscriminate eradication recommended in some guidelines.[39]

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Conflicts of interest

None.

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