**Abstract**

*Helicobacter pylori* has coexisted with humans for approximately 60,000 years and greater than 50% of the global population is infected with *H. pylori*. *H. pylori* was successfully cultured in vitro in 1983 and studies of *H. pylori* have achieved substantial advances over the last 35 years. Since then, *H. pylori* has been characterized as the primary pathogenic factor for chronic gastritis, peptic ulcer, and gastric malignancy. Numerous patients have received *H. pylori* eradication treatment, but only 1–2% of *H. pylori*-infected individuals ultimately develop gastric cancer. Recently, numerous epidemiological and basic experimental studies suggested a role for chronic *H. pylori* infection in protecting against inflammatory bowel disease (IBD) by inducing systematic immune tolerance and suppressing inflammatory responses. Here we summarize the current research progress on the association between *H. pylori* and IBD, and further describe the detailed molecular mechanism underlying *H. pylori*-induced dendritic cells (DCs) with the tolerogenic phenotype and immunosuppressive regulatory T cells (Tregs). Based on the potential protective role of *H. pylori* infection on IBD, we suggest that the interaction between *H. pylori* and the host is complicated, and *H. pylori* eradication treatment should be administered with caution, especially for children and young adults.

**Facts**

- IBD etiology is mainly attributed to the complex interaction between immune dysfunction, host genetic susceptibility, and environmental factors.
- Epidemiological and basic experimental studies both suggested a protective role of chronic *H. pylori* infection against IBD.
- This protective effect on IBD could be attributed to *H. pylori*-induced systematic immune tolerance and the suppression of inflammatory response.
- Tolerogenic phenotype DCs and immunosuppressive Treg are thought to be involved in the protective mechanisms.
- Low bioactive LPS of *H. pylori* could not effectively activate NF-kB pathway and stimulate the secretion of proinflammatory factors. IL-10, TGF-β, NLRP3 inflammasome, and IL-18 are critical for the protective effect of *H. pylori* on IBD.

**Open questions**

- Multicenter cohort studies revealing the status of *H. pylori* infection immediately after diagnosis of IBD is highly desirable.
- Prospective studies focusing on the pathogenesis or progression of IBD after *H. pylori* eradication therapy is urgently needed.
- The relationship between enterohepatic helicobacteria species and IBD needs to be further revealed.
- The detailed molecular mechanism underlying *H. pylori* infection and IBD needs to be further discussed.
pylori-induced tolerogenic phenotype DCs and immunosuppressive Tregs is not yet clear.

- Considering the trade-off between gastric cancer prevention and the risk of triggering of IBD, whether an asymptomatic H. pylori infection should be provided with an eradication prescription is still worth discussing.

Introduction

Inflammatory bowel disease (IBD) is characterized by chronic, nonspecific intestinal inflammation with an unexplained pathology and an alternating relapsing and remitting clinical progression. IBD is divided into two subtypes: ulcerative colitis (UC) and Crohn’s disease (CD). The pathological features of IBD include enhanced TH1 and/or TH17 responses, and dramatically increased production of inflammatory factors in mucosal lesions, including tumor necrosis factor-α, interleukin (IL)-1β, interferon (IFN)-γ, IL-17, IL-6, and IL-23. Most studies in the IBD field attribute its etiology to the complex interactions among immune dysfunction, genetic susceptibility of the host, and environmental risk factors. Autoimmune abnormalities are now widely considered one of the causes of IBD. Most patients with IBD have an individual or family history of nodular erythema, arthritis, ophthalmic uveitis, vasculitis, or systemic lupus erythematosus. In addition, mutants in autophagy genes (ATG16L1/NOD2/IRGM) were identified as inducers of aberrant immunopathological responses and impair the mucosal barrier. In the last two decades, the role of Helicobacter species in IBD pathogenesis has been widely discussed. H. pylori gastritis Kyoto global consensus report, H. pylori gastritis should be defined as an “infectious disease” and all H. pylori-positive patients should receive eradication therapy, regardless of the presence of gastric ulcers or gastric cancer. However, although approximately half of the global population is infected with H. pylori, only 10–20% of H. pylori-infected individuals exhibit peptic ulcers, 1–2% develop gastric cancer, and < 1% exhibit gastric mucosa-associated lymphoid tissue lymphoma. Moreover, consistent with “Africa enigma,” recently reported gastric cancer prevalence is also much lower in less developed Asian countries (who have high H. pylori infection rates range of 55–92%) than relatively developed Asian country.

Association between H. pylori and IBD

Recently, emerging epidemiologic studies and animal experiments revealed an inverse correlation between H. pylori infection and IBD onset, suggesting that H. pylori colonization exerts a special protective effect on autoimmune diseases. Since the twenty-first century, improving hygienic conditions and socioeconomic status have reduced the H. pylori infection rate and this trend has concurrently been accompanied by an increased IBD incidence in most countries. Most experts in the IBD field interpret this phenomenon based on the “hygiene hypothesis”: H. pylori infection during childhood contributes to immune system development and may prevent the onset of autoimmune or allergic diseases. Moreover, due to the initiation of H. pylori eradication for peptic ulcers, the incidence of IBD has increased steadily in these regions. Further clarification of the protective effect of H. pylori on IBD and the underlying mechanism will be important for H. pylori infection management strategies and the treatment and prevention of IBD (Fig. 1 and Fig. 2).

Enterohemorrhagic helicobacteria participate in IBD pathogenesis

Various non-pylori Helicobacter organisms in the Helicobacteraceae family have been found to be able to colonize throughout the gastrointestinal tract and are defined as enterohemorrhagic helicobacteria species (EHS). In addition, 16s rDNA sequencing of colonic biopsies and fecal samples revealed an increased prevalence of the Helicobacteraceae family in children with CD,
particularly Helicobacter bilis and Helicobacter hepaticus. A meta-analysis further revealed an increased prevalence of EHS among patients with IBD compared with the control group (RR(relative risk) = 2.01, 95% confidence interval (CI): 1.36–2.98). In fact, some EHS have been routinely used to induce experimental colitis in immunodeficient animals. In a study on the pathogenic mechanism of EHS by Kullberg et al., H. hepaticus infection elicited persistent colitis in IL-10−/− mice by stimulating an IL-12(p35/P40)-dependent Th1 reaction. Subsequently, Kullberg et al. further verified that the IL-23(P40/P19)-dependent Th17 reaction also played a key role in an H. hepaticus-induced mouse colitis model. Other pathogenic mechanisms reported in related studies include disruption of the intestinal epithelial integrity by the type VI secretion system, disruption of the eukaryotic cell cycle via the production of a cytolytic distending toxin, and alterations in normal flora colonization to reduce flora diversity. Based on these findings, intestinal Helicobacteraceae colonization is a potentially pathogenic factor for IBD, not a protective factor.

**The potential protective effect of H. pylori infection on IBD**

Numerous studies have reported a lower H. pylori infection rate in patients with CD and/or UC than in non-IBD control individuals, although a small number of studies showed no significant association (Table 1). The inverse correlation between IBD and H. pylori infection suggests that the gastric mucosa colonization of H. pylori can potentially protects against the pathogenesis of IBD via a special mechanism. Two meta-analyses (including 23 and 33 studies, separately) provide more powerful evidence supporting this protective effect of H. pylori infection on the prevalence of IBD.
However, the significant heterogeneity among the included studies and the potential publication bias largely limited the confidence of this negative correlation. Differences in *H. pylori* detection methods, IBD diagnostic criteria, study sites, participant ages, and histories of antibiotic therapy potentially contribute to the severe heterogeneity, which was not resolved by a subgroup analysis. However, a recent meta-analysis without statistical heterogeneity and publication bias also reported an inverse correlation (RR = 0.48, 95% CI: 0.43–0.54) between *H. pylori* infection and IBD prevalence in an Asian population (Table 2).

Some researchers attributed this inverse correlation to the complex medical therapies used by patients with IBD, including metronidazole, quinolone drugs, sulfasalazine, 5-aminosalicylic acid, corticosteroids, and immunosuppressants. The intake of these medications was considered a possible cause of the “spontaneous eradication” effect that leads to the low *H. pylori* infection rate in patients with IBD. However, this conclusion was not supported by other studies, which reported that a history of taking sulfasalazine, 5-aminosalicylic acid, corticosteroids, and immunosuppressants was not a confounding factor for this inverse correlation. In addition, even if antibiotics reduce *H. pylori* infection rates in patients with IBD, the *H. pylori* infection rate remains significantly reduced in patients with IBD without a history of antibiotics use compared with healthy controls. Multicenter prospective cohort studies...
Table 1  Prevalence of *H. pylori* infection in patients with IBD compared with the control population

| Author                  | IBD                      | NC                      | $\chi^2$ | $p$-Value | HP test   | Control selection       | Year | Country |
|-------------------------|--------------------------|-------------------------|----------|-----------|-----------|-------------------------|------|---------|
|                         | $H. pylori$ (+) N (%)    | $H. pylori$ (-) N (%)   |          |           |           |                         |      |         |
| Halme et al.44          | 30 (15%)                 | 170 (85%)               | 28.3869  | < 0.0001  | $H. pylori$ IgG (+)     | Patients with acute dysentery | 1996 | Finland |
| Pearce et al.45         | 16 (17.2%)               | 77 (82.8%)              | 1.0808   | 0.2985    | UBT*       | IBS                     | 2000 | UK      |
| Sukerek et al.46        | 2 (5.3%)                 | 36 (94.7%)              | 1.4164   | 0.2340    | IHC* staining | NR*                    | 2001 | USA     |
| Väre et al.47           | 67 (24%)                 | 212 (76%)               | 4.9344   | 0.0263    | $H. pylori$ IgG (+)     | NR               | 2001 | Finland |
| Matsumura et al.48      | 15 (16.7%)               | 75 (83.3%)              | 18.2909  | < 0.0001  | $H. pylori$ IgG (+)     | Healthy volunteers            | 2001 | Japan   |
| Feeney et al.49         | 26 (9.4%)                | 250 (90.6%)             | 4.7864   | 0.0287    | $H. pylori$ IgG (+)     | Non-IBD patients            | 2002 | UK      |
| Parlak et al.50         | 74 (66.7%)               | 37 (33.3%)              | 0.1846   | 0.6675    | IHC staining          | Non-IBD patients            | 2002 | Turkey  |
| Prómai et al.51         | 17 (12.8%)               | 116 (87.2%)             | 26.9294  | < 0.0001  | UBT        | Non-IBD patients         | 2004 | Hungary |
| Sladek et al.52         | 9 (9.6%)                 | 85 (90.4%)              | 22.1234  | < 0.0001  | UBT        | Non-IBD patients         | 2006 | Poland  |
| Song et al.53           | 80 (25.3%)               | 236 (74.7%)             | 49.23    | < 0.0001  | UBT        | Healthy volunteers       | 2009 | Korea   |
| Pang et al.54           | 33 (81.1%)               | 73 (18.9%)              | 19.4314  | < 0.0001  | $H. pylori$ IgG (+)     | Healthy volunteers            | 2009 | China   |
| Li et al.55             | 13 (26%)                 | 37 (74%)                | 9.3024   | 0.0023    | UBT        | Non-IBD patients         | 2010 | China   |
| Pellicano et al.56      | 12 (60%)                 | 8 (40%)                 | 1.6423   | 0.2000    | UBT        | Non-IBD patients         | 2010 | Italy   |
| Zhang et al.57          | 40 (19.2%)               | 168 (80.8%)             | 50.98    | < 0.0001  | UBT        | Healthy volunteers       | 2011 | China   |
| Sonnenberg and Genta58  | 48 (4.5%)                | 1016 (95.5%)            | 25.9461  | < 0.0001  | IHC staining | Healthy volunteers       | 2011 | USA     |
| Xiang et al.59          | 62 (27.1%)               | 167 (72.9%)             | 22.1069  | < 0.0001  | UBT        | Non-IBD patients         | 2013 | China   |
| Jin et al.60            | 47 (30.5%)               | 106 (69.5%)             | 19.1521  | < 0.0001  | UBT        | Non-IBD patients         | 2013 | China   |
| Xin et al.61            | 33 (18.4%)               | 146 (81.6%)             | 17.5774  | < 0.0001  | UBT        | IBS                    | 2013 | China   |
| Ali et al.62            | 6 (1.7%)                 | 341 (98.3%)             | 23.4916  | < 0.0001  | IHC staining | Non-IBD patients         | 2013 | United States |
| Roka et al.63           | 6 (3.8%)                 | 153 (96.2%)             | 11.7957  | 0.0006    | UBT        | Non-IBD patients         | 2014 | Greece  |
| Ma et al.64             | 38 (47.5%)               | 42 (52.5%)              | 5.7334   | 0.0166    | UBT        | Healthy volunteers       | 2016 | China   |
| Shi et al.65            | 114 (69.0%)              | 51 (30.1%)              | 33.0582  | < 0.0001  | UBT        | Non-IBD patients         | 2017 | China   |
| Zhou et al.66           | 19 (32.8%)               | 39 (67.2%)              | 15.1143  | 0.0001    | UBT        | Non-IBD patients         | 2017 | China   |

*IBD* inflammatory bowel disease, *IHC* immunohistochemistry, *NR* not reported by Kaakoush, *UBT* urea breath test
that confirm the *H. pylori* infection status and therapy history immediately after IBD diagnosis are urgently needed, and better control of confounding factors in these studies should be implemented to achieve definitive conclusions.

Animal experiments also confirmed the negative correlation between *H. pylori* infection and IBD onset. As shown in the study by Fen et al.76, *H. pylori* infection significantly ameliorates colitis and histopathological changes in a DSS-induced mouse colitis model. This pathological difference is accompanied by reductions in splenic CD4+ T cells and the extent of systemic inflammation. Using mice co-infected with *H. pylori* and *Salmonella typhimurium*, Higgins PD77 reported that *H. pylori* inhibits the Th17 response to *S. typhimurium* infection and increases IL-10 levels in mesenteric lymph nodes. Based on the results of these studies, *H. pylori* infection affects the immune response in the lower digestive tract and involves potential immunological crosstalk between the upper and lower gastrointestinal tracts.

**Table 2  Meta-analysis of *H. pylori* infection rates in patients with IBD**

| Author                  | Subgroup | Pooled RR/OR | 95% CI      | p-Value | Heterogeneity | Publication bias |
|-------------------------|----------|--------------|-------------|---------|---------------|-----------------|
|                         |          |              |             |         |               |                 |
| Luther et al.67         | IBD      | 0.64         | 0.54–0.75   | NR      | 75.80%        | <0.001 NR       |
|                         | CD       | 0.6          | 0.40–0.72   | NR      | NR            | NR              |
|                         | UC       | 0.75         | 0.62–0.90   | NR      | NR            | NR              |
| Rokkas et al.68         | IBD      | 0.62         | 0.55–0.71   | <0.001  | 77%           | <0.001 0.15     |
|                         | CD       | 0.38         | 0.31–0.47   | <0.001  | 59.50%        | <0.001          |
|                         | UC       | 0.53         | 0.42–0.67   | <0.001  | 62%           | <0.001          |
| Wu et al.69             | IBD      | 0.48         | 0.43–0.54   | <0.001  | 21%           | NR              |
|                         | CD       | 0.43         | 0.37–0.50   | <0.001  | 43.00%        | NR              |
|                         | UC       | 0.55         | 0.48–0.64   | <0.001  | 0%            | NR              |
| Castañorodríguez et al.74 | IBD    | 0.426        | 0.362–0.502 | <0.001  | 62%           | <0.001 NR       |
|                         | CD       | 0.38         | 0.31–0.47   | <0.001  | NR            | NR              |
|                         | UC       | 0.53         | 0.44–0.65   | <0.001  | NR            | NR              |

CD Crohn’s disease, CI confidence interval, IBD inflammatory bowel disease, OR odds ratio, UC ulcerative colitis

**H. pylori infection induces tolerogenic DCs**

Dendritic cells (DCs) capture *H. pylori* antigens in the gastric cavity

Although numerous epidemiological studies and meta-analyses support the inverse correlation between *H. pylori* infection and IBD onset, the protective mechanism by which the upper digestive tract colonization of *H. pylori* can protect against IBD remains unclear. As the most powerful antigen-presenting cell and the unique activator of naive T lymphocytes (Th0), DCs have a key role in modulating adaptive immunity through the presentation of pathogen antigens and induce Th0 cells to differentiate into different lymphocyte subsets. Using two-photon microscopy to observe transgenic pCD11c-YFP mice, Kao et al.78 reported that CD11c+ DCs are located near the gastric luminal surface and submucosal layer, and the number of DCs in the lamina propria was dramatically increased and DCs moved closer to the epithelial surface after *H. pylori* infection. Moreover, through a three-dimensional co-culture system that includes monocytes, DCs and a Caco-2 cell monolayer in a type I bovine collagen system, Leonard et al.79 observed DCs can move to the surface of Caco-2 cell monolayer or integrated with it. These studies indicated DCs can migrate through the intestinal epithelium to sense gastrointestinal tract antigens without impairing the integrity of the epithelial barrier.

**H. pylori remodel DCs to exhibit an immune tolerance property**

Investigations focused on the tolerogenic property of *H. pylori*-specific DCs may help reveal the intriguing mechanism by which *H. pylori* induces systematic immunosuppression. Oertli et al.80 purified gastric mucosa lamina propria-derived DCs from *H. pylori*-infected patients and found that these DCs express high levels of HLA-DR and SIGN but low levels of CD80, CD83, and CD86. Kao et al.78 further studied the different cytokines secreted by bone marrow-derived DCs after stimulation with *H. pylori*, *Escherichia coli*, and Ruffey’s
**Acinetobacter**. In this study, *H. pylori*-stimulated DCs not only maintained high transforming growth factor (TGF)-β levels but also displayed lower levels of IL-6 and IL-23 expression level than DCs stimulated with the other two positive control bacteria. IL-6 and IL-23 are important inflammatory factors that have key roles in Th17 differentiation and function maintenance,

\[ H. pylori \]

suggesting that *H. pylori* has a poor pathogenicity that cannot effectively activate the inflammation pathway and Th17-modulated proinflammatory responses. This tolerogenic property also has been observed at the level of DC surface molecules. In the study by Oertli et al.,

\[ H. pylori \]

prestimulate DCs with *H. pylori* in vitro significantly suppressed the *E. coli* lipopolysaccharide (LPS)-induced upregulation of CD80, CD86, and CD40. In addition, significantly lower IL-12 p40 and IL-6 levels were observed in *H. pylori*-prestimulated DCs than in the *E. coli* LPS-treated group (summarized schematically in Figure 1). Based on these evidence, although *H. pylori* infection recruits numerous DCs to the gastric mucosa, these DCs exhibit a functionally semi-mature status with an immune tolerance phenotype. This immune tolerance property of *H. pylori* may contribute to its persistent colonization of the gastric mucosa and its ability to simultaneously exert a systematic immunomodulatory effect to suppress autoimmune immunopathological responses.

**Molecular mechanism by which *H. pylori* induces tolerogenic DCs**

The intrinsic nature of immune tolerance induced by *H. pylori* is attributed to the low bioactivity of its LPS. By administering intravenous injections of different LPS doses and performing three typical in vitro endotoxin tests, Muotiala et al.

\[ H. pylori \]

observed an approximately 500- to 1000-fold reduction in the biological activation of *H. pylori* LPS compared with two *Salmonella enterica* serovar *Typhimurium* subspecies (Figure 2). Long 3-hydroxy fatty acids and a deficiency of phosphorylated groups at position 4' in the β-glucosamine disaccharide backbone of Lipid A, a constituent component of LPS, potentially explain the reduced biological activity. This uncommon structure and the significantly weaker biological activation of *H. pylori* LPS may be responsible for the formation of tolerogenic semi-mature DCs. In addition, modifications in the N-terminal TLR5 recognition domain of *H. pylori* flagellin may contribute to the escapes recognition by TLR5 (Figure 2). *H. pylori* induces DC proliferation and activates autophagosome formation in vitro. *H. pylori* infection-induced autophagy activity may participate in DC remodeling process; LC3, LAMP1, and major histocompatibility complex (MHC) class II molecules were found retained in autophagic vacuoles after *H. pylori* infection; meanwhile, the surface expression of MHC II, CD80, and CD86 decreases in a TLR2/TLR4-dependent manner. Moreover, no IL-12 was detected in DCs stimulated with wild-type or VacA/CagA mutant *H. pylori* strains consistent with the downregulation of DC function and impaired T-cell proliferation (Figure 2). Based on these results, *H. pylori* infection induces TLR2/TLR4-dependent autophagy to downregulate DC function and inhibit T-cell proliferation. However, the detailed mechanism by which *H. pylori* participates in the interaction between autophagy activation and inflammatory pathways remains to be further elucidated. Moreover, some virulence factors may be necessary for the protective effect of *H. pylori* on IBD and asthma. Lord et al. reported a significantly lower CagA-positive rate in patients with CD (0.94%) than in unaffected individuals (7.48%), suggesting that the CagA protein may participate in the IBD protective mechanism. Oertli et al. and Engler et al. demonstrated two dominant virulence factor γ-glutamyl transpeptidase and VacA were essential for *H. pylori*-induced tolerogenic re-programming of DCs in vivo and in vitro asthma model. However, contradictory conclusions were obtained from colitis animal model; in these studies, the immunomodulatory effect of *H. pylori*-stimulated DCs was independent of VacA or CagA.

**H. pylori infection induces immunosuppressive Tregs**

Tregs participate in *H. pylori*-induced immune tolerance

As *H. pylori* strictly colonizes the gastric mucosa, the mechanism by which *H. pylori* remotely modulates lower digestive tract immune responses to influence the pathogenesis of IBD is still a subject of debate. Recently, emerging animal and in vitro experiments provided thought-provoking evidence that *H. pylori* infection of the upper digestive tract can modulate the systemic immune response by remodeling DCs to exhibit immune tolerance properties and subsequently induce Tregs polarization. Tregs are one lymphocyte subgroup that suppresses the activity of effector T cells and has a key role in maintaining immune system homeostasis and self-tolerance. Forkhead box transcription factor (FOXP3) expression is required for this immunosuppressive function of Tregs. Foxp3-expressing regulatory B cell can upregulate Treg/Th17 ratio to ameliorate autoimmune arthritis. Foxp3-knockout mice develop various severe or even fatal metabolic, allergic, and autoimmune diseases. Tregs can suppress effector T-cell differentiation and proliferation by direct contact inhibition or anti-inflammatory cytokine secretion. Moreover, Tregs was shown can diminish the upregulation of costimulatory molecule on splenic DCs. Tregs also participate in the pathogenesis of *H. pylori*-induced chronic gastritis and many studies report increased numbers of CD4 + CD25 + Foxp3 + Tregs in...
the gastric mucosa of patients with *H. pylori* infections. Transfer of Tregs derived from *H. pylori*-pretreated neonatal mice donor attenuated ovalbumin-induced allergic airway inflammation when compared with challenged control mice. Conversely, systemic Treg depletion abolished this protection effect. More evidence was reported by Kao et al.; they stimulated MACS(Magnetic Activated Cell Sorting) microbead-isolated splenic CD4+ T cells with bone marrow-derived DCs and *H. pylori* SS1 in vitro, and found that *H. pylori* induces an increased Treg ratio and decreases IL-17 levels in an IL-10- and TGF-β-dependent manner. Moreover, adoptive transfer of *H. pylori* SS1-stimulated DCs in mice induces a peripheral *H. pylori*-specific Treg response that is characterized by increased IL-10 secretion from splenic CD4+ T cells. Thus, *H. pylori*-stimulated DCs can subsequently promote Treg differentiation to induce immune tolerance.

**Tregs have a key role in systematic immunomodulation**

As Tregs are required to prevent dysfunctional inflammatory responses to commensal organisms in the lower digestive tract, Tregs may have a central role in chronic *H. pylori* infection-induced systematic immunomodulation and exert protective effects on IBD. This hypothesis was further verified by the effectiveness of Treg adoptive transfer therapy on mouse models of colitis or asthma. In contrast, the dramatically reduced *H. pylori* colonization density after Treg depletion was accompanied by an enhanced peripheral Th17 response in response. In addition, *H. pylori*-positive patients typically present with lower peripheral type 1 IFN levels than the control group. Based on the lymphocyte recirculation theory, we proposed that although *H. pylori* strictly colonizes the gastric mucosa, *H. pylori*-induced Tregs arrive at remote organs to suppress effector T-cell proliferation and elicit a systemic immunoregulatory effect. Furthermore, Onishi et al. found Tregs can aggregate around DCs and subsequently downregulate the costimulatory molecules CD80 and CD86 to maintain the semi-mature phenotype of DCs. Together with the lymphocyte recirculation theory, these findings explain the increase in the lung infiltration of semi-mature DCs in *H. pylori*-infected mice, as *H. pylori* is unlikely to directly influence the respiratory system. In conclusion, the considerable number of Tregs induced by persistent *H. pylori* colonization in the upper digestive tract may exert a systematic immunoregulatory effect on remote organs via lymphocyte recirculation and might ultimately influence the pathogenesis of various autoimmune and allergic diseases, such as IBD and asthma.

**Molecular mechanism by which *H. pylori* induces immunosuppressive Tregs**

TGF-β and IL-10 are two important and well-recognized immunoregulatory factors, and these molecules are associated with IBD onset and Treg-modulated intestinal mucosal homeostasis, which suggest that tolerogenic DCs may induce and maintain Treg differentiation via IL-10- and TGF-β-dependent mechanisms. Pretreatments with TGF-β and IL-10-neutralizing antibodies reversed the ameliorated colitis pathology and the upregulation of Treg/Th17 ratio after *H. pylori* stimulation further proved this hypothesis. Intestinal epithelial cells derived from IL-10−/− mice only express RelA (p65, a phosphorylated nuclear factor (NF)-κB subunit), but not phosphorylated Smads, after pathogen stimulation. Meanwhile, TGF-β was shown to activate Smad signaling to inhibit Toll-like receptor (TLR) expression and NF-κB pathway-related proinflammatory cytokine secretion. In addition, Engler et al. revealed a significant correlation among CDX2, MUC2, and TGF-β, and demonstrated the activation of the TGF-β-dependent Smad-CDX2-MUC2 axis after *H. pylori* infection or extraction treatment can increases intestinal mucus secretion and ameliorate experimental colitis (summarized schematically in Figure 2). In summary, these evidences indicated TGF-β and IL-10 are critical factors for Treg differentiation and activation of protective Smad signaling after bacterial pathogen stimulation. *H. pylori* can be successfully sensed by TLR2/NOD2 and subsequently activate NLRP3 inflammasome and caspase-1 to promote the maturation of IL-1β and IL-18. The essential role of NLRP3 inflammasome and IL-18 for the protective effect of *H. pylori* on experimental colitis was proved by Engler et al. They found Nlrp3−/−, IL-18−/−, and IL18R−/− deficient mice all lack the effective protective effect of a live *H. pylori* oral infection or intraperitoneal injection of extracts. Moreover, IL-18 was found to be required for Treg differentiation in vivo and in vitro. LPS was previously shown to activate NF-κB pathway and significantly promote pro-IL-1β transcription to induce Th17 differentiation and stimulate powerful inflammatory response.

Although LPS also induces pro-IL-18 processing via the NLRP3 inflammasome, this process occurs independently of NF-κB activation due to stable storage of pro-IL-18 in cytoplasmic granules. Therefore, the inefficient perception by TLR4 and diminished NF-κB pathway due to low activity of *H. pylori* LPS lead to decreased pro-IL-1β and IL-1β levels, but not for IL-18 expression (summarized schematically in Figure 2). As IL-1β has been shown to be a strong proinflammatory cytokine, the alterations in the relative expression levels of IL-1β and IL-18 may strikingly skew the Th1/Th17-dominated response.
proinflammatory response to a Treg-dominated immunosuppressive response.

The crosstalk between HP eradication and the immune response

Although *H. pylori*-associated gastroenteritis is characterized by the aggregation of local lymphocytes and polymorphonuclear cells, *H. pylori* can persistently colonize the gastric mucosa, depending on its immune escape mechanism. According to previous studies, relatively mild gastritis in children is typically accompanied by higher levels of the Foxp3 mRNA and regulatory cytokine (IL-10 and TGF-β) expression, as well as decreased levels of the IL-17 mRNA and neutrophil infiltration in the gastric mucosa than adults with more severe gastritis. Neonatally infected mice exhibit higher density of *H. pylori* colonization due to the lack of CD4+ T-cell infiltration into the gastric mucosa. Meanwhile, neonatally infected mice derived DCs incompetently inducing Th1 effector responses from naïve T cells than adult-infected group. Furthermore, in a DSS-induced colitis mouse model, mice infected during neonatal period showed less pathology and less proinflammatory cytokine secretion. These finding can be attributed to the different pathogenicity sense ability and CD4+ T-cells differentiation tendency between children and adult. Above evidences indicate young people whose immune system may still get remodeled can benefit more from the immune tolerance induced by *H. pylori* than older people. Another intriguing phenomenon is the significantly higher success rate of *H. pylori* clearance in patients with ulcers compared with patients with chronic gastritis. A reasonable interpretation is the immune tolerogenic property of *H. pylori*, which acquired in the long co-evolution history with human, can polarize adaptive immune to Foxp3+ Treg-dominated immunoregulatory response to favor its persistent colonization. Given the large number of Tregs and their immunosuppressive properties, patients with chronic gastritis cannot elicit a sufficiently effective immune response to eradicate *H. pylori*. However, in patients with ulcers, the breakdown of the balance between Tregs and Th1/Th17 cells transform the immune system to the latter dominating proinflammatory response, leading to more severe pathological lesions. Meanwhile, *H. pylori* is easier to eradicate using exogenous antibiotic and proton pump inhibitor treatments. Moreover, given the role of Tregs in the immune evasion strategies for some specific pathogens, Tregs depletion has been shown to elicit aggravated gastric mucosal inflammation and bacterial clearance in *H. pylori*-infected mice in vivo.

In addition, *H. pylori* eradication therapy may trigger the onset of IBD. However, the evidence supporting this hypothesis is limited and inconclusive, because limited supportive data are available. One case report from Jovanovic et al. examined one 28-year-old male patient who received 2 weeks of eradication therapy for ulcer-like dyspepsia symptoms. Six months after therapy, he experienced crampy abdominal pain, mild periodical fever, and watery diarrhea, and an endoscopic examination revealed segmental stenotic and Crohn’s-like lesions in the upper portion of the small intestines. In addition, Turzi reported two severe cases of CD (one in the terminal ileitis and one in the cecum and ascending colon) with multiple ulcers and full-thickness lymphoid infiltrates after *H. pylori* eradication therapy. The authors hypothesized that the breakdown of the equilibrium between the Th1 and Th2 responses and subsequent Th1 polarization might favor the onset of CD in some genetically susceptible individuals. However, in a small-sample *H. pylori* eradication cohort study of six patients with quiescent CD, statistically significantly differences in the CDAI (CD activity index), CRP (C-Reactive protein), and fecal calprotectin levels were not observed after *H. pylori* eradication. Further studies are urgently needed to reveal the relationship between *H. pylori* eradication and IBD onset or progression.

Perspectives

Almost all patients with *H. pylori* infection exhibit chronic inflammation in the gastric mucosa, causing *H. pylori* to be defined as an infectious pathogen according to Koch’s law. As *H. pylori*-induced chronic atrophic gastritis is a crucial risk factor for gastric cancer, the Kyoto global consensus suggests that all *H. pylori*-infected individuals should be treated with eradication unless they present with contraindications to this treatment. Overall, eradication of *H. pylori* has not been confirmed by China’s national guidelines, considering the high infection rate and large quantities of antibiotics administered. In fact, the overall effects besides increased gastric cancer risk were largely ignored by the epidemiologists dedicated in *H. pylori* control. During the long co-evolutionary process with humans, *H. pylori* developed an immune tolerance property that favors its persistent mucosal colonization and simultaneously regulates systematic immune homeostasis by inducing tolerogenic DCs and immunosuppressive Tregs. Thus, the eradication of *H. pylori* with antibiotics not only largely influences the homeostasis of gut microbes but also has an indirect but profound effect on immune homeostasis and may lead to various autoimmune and allergic diseases, such as IBD and asthma. Just as we could not evaluate the gastric cancer risk in *H. pylori*-infected individuals accurately, we also could not perfectly evaluate the risk of IBD after *H. pylori* eradication, especially for IBD susceptible gene carriers. In conclusion, the immune tolerance property of *H. pylori*...
should be thoroughly considered when designing optimized and individualized treatments for H. pylori-infected patients.

Acknowledgements
This work was completely supported by grants from the National Natural Science Foundation of China (81570507 and 81702314) and Funding Program for Excellent Talents of Beijing (201700021469G212).

Conflict of interest
The authors declare that they have no conflict of interest.

Publisher’s note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References
1. Baumgart, D. C. & Sandborn, W. J. Crohn’s disease. Lancet 380, 1590–1605 (2012).
2. Oda, S., Edsman, L., Talimini, M., Baumgart, D. C. & Sandborn, W. J. Ulcerative colitis. Lancet 380, 1606–1619 (2012).
3. Manichanh, C., Borneuil, N., Casellas, F. & Guarner, F. The gut microbiota in IBD. Nat. Rev. Gastroenterol. Hepatol. 9, 599–608 (2012).
4. Justins, L. et al. Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease. Nature 491, 119–124 (2012).
5. Fujino, S. et al. Increased expression of interleukin 17 in inflammatory bowel disease. Gut 52, 65 (2003).
6. Hoe, S. et al. Interleukin-23 drives innate and T cell-mediated intestinal inflammation. J. Exp. Med. 203, 2473–2483 (2006).
7. First, G. et al. Differential regulation of interleukin-17 and interferon-γ production in inflammatory bowel disease. Dig. Liver Dis. 58, 1629 (2009).
8. Song, T. D. & Zhong, H. Relationship between autophagy abnormalities and pathogenesis of inflammatory bowel disease. Chin. J. Gastroenterol. 22, 304–307 (2017).
9. Thia, K. T. et al. An update on the epidemiology of inflammatory bowel disease in Asia. Ann. J. Gastroenterol. 103, 3167–3182 (2008).
10. Sekisl, P. Gut microbiota and IBD. Gastroenterol. Clin. Biol. 34, 544 (2010).
11. Johnson, L. D. et al. A prospective study of the epidemiology of colitis and colon cancer in cotton-top tamarins (Saguinus oedipus). Gastroenterology 110, 102–115 (1996).
12. Selton, R. K. et al. Resident enteric bacteria are necessary for development of spontaneous colitis and immune system activation in interleukin-10-deficient mice. Infect. Immun. 66, 5224 (1998).
13. Baumgart, D. C. et al. IBD around the world comparing the epidemiology, diagnosis, and treatment proceedings of the World Digestive Health Day 2010-Inflammatory Bowel Disease Task Force meeting. Inflamm. Bowel Dis. 17, 639–644 (2011).
14. Molodecky, N. A. et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. Gastroenterology 142, 46–54 (2012).
15. Loftus, E. V. Clinical epidemiology of inflammatory bowel disease: incidence, prevalence, and environmental influences. Gastroenterology 126, 1504–1517 (2004).
16. Xavier, R. J. & Podolsky, D. K. Unravelling the pathogenesis of inflammatory bowel disease. Nature 448, 427 (2007).
17. Zhao, J. et al. First prospective, population-based inflammatory bowel disease incidence study in mainland of China the emergence of “western” disease. Inflamm. Bowel Dis. 14, 1839–1845 (2013).
18. Kaplan, G. G. et al. Globalisation of inflammatory bowel disease: perspectives from the evolution of inflammatory bowel disease in the UK and China. Lancet Gastroenterol. Hepatol. 1, 307 (2016).
19. Ng, S. C. et al. Incidence and phenotype of inflammatory bowel disease based on results from the Asiapacific Crohn’s and colitis epidemiology study. Gastroenterology 145, E2 (2013).
20. Ye, L., Cao, Q., Cheng, J. Review of inflammatory bowel disease in China. Sci. World J. 2013, 296470 (2013).
21. Dunn, B. E., Cohen, H. & Blaser, M. J. Helicobacter pylori. Clin. Microbiol. Rev. 10, 720–741 (1997).
22. Warren, J. R., Marshall, B. Unidentified cored bacilli on gastric epithelium in active chronic gastritis. Lancet 1, 1273–1275 (1983).
23. Dooley, C. P. et al. Prevalence of Helicobacter pylori infection and histologic gastritis in asymptomatic persons. New Engl. J. Med. 321, 1562–1566 (1989).
24. Marshall, B. J. & Warren, J. R. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. Lancet 1, 1311 (1984).
25. Sugano, K. et al. Kyoto global consensus report on Helicobacter pylori. Gut 64, 1353–1367 (2015).
26. Parsonnet, J. et al. Helicobacter pylori infection and the risk of gastric carcinoma. N. Engl. J. Med. 325, 1127–1131 (1991).
27. Parsonnet, J. et al. Helicobacter pylori infection and gastric lymphoma. N. Engl. J. Med. 330, 1267–1271 (1994).
28. Kusters, J. G., van Vliet, A. H. & Kuipers, E. J. Pathogenesis of Helicobacter pylori infection. Clin. Microbiol. Rev. 19, 449–490 (2006).
29. Singh, K. & Ghoshal, U. C. Causal role of Helicobacter pylori infection in gastric cancer: an Asian enigma. World J. Gastroenterol. 12, 1346–1351 (2006).
30. Arnold, I. C., Iris, H. & Anne, M. The immunomodulatory properties of Helicobacter pylori confer protection against allergic and chronic inflammatory disorders. Front. Cell. Infect. Microbiol. 2, 10 (2012).
31. Aherton, J. C., Blaser, M. J. Helicobacter pylori infections. In: Hanson’s Principles of Internal Medicine 16th ed, pp 88828 (McGraw-Hill, New York, 1998, 2005).
32. Zhang, L., Day, A., McKenzie, G. & Mitchell, H. Nongastric Helicobacter species detected in the intestinal tracts of children. J. Clin. Microbiol. 44, 2276–2279 (2006).
33. Oliveira, A. G. et al. Isolation of Helicobacter pylori from the intestinal mucosa of patients with Crohn’s disease. Helicobacter 11, 2–9 (2006).
34. Streeker, C. J., Bernstein, C. N., Chan, V. L., Riddell, R. H. & Croitoru, K. Detection of species-specific Helicobacter ribosomal DNA in intestinal biopsy samples from a population-based cohort of patients with ulcerative colitis. J. Clin. Microbiol. 42, 660–664 (2004).
35. Man, S. M., Zhang, L., Day, A. S., Leach, S. & Mitchell, H. Detection of enterohemorrhagic and gastric Helicobacter species in fecal specimens of children with Crohn’s disease. Helicobacter 13, 234–238 (2008).
36. Yu, Q. et al. Enterohemorrhagic Helicobacter species as a potential causative factor in inflammatory bowel disease: a meta-analysis. Medicine 94, e173 (2015).
37. Hansen, R., Thomson, J. M., Fox, J. G., El-Omar, E. M. & Hold, G. L. Could Helicobacter organisms cause inflammatory bowel disease? FEMS Immunol. Med. Microbiol. 61, 1–14 (2011).
38. Kullberg, M. et al. Helicobacter hepatitis triggers colitis in specific-pathogen-free interleukin-10 (IL-10)-deficient mice through an IL-12 and gamma interferon dependent mechanism. Infect. Immun. 66, 5157–5166 (1998).
39. Kullberg, M. C. et al. IL-23 plays a key role in Helicobacter hepaticus-induced T cell-dependent colitis. J. Exp. Med. 203, 2485–2494 (2006).
40. Chow, J. & Mazmanian, S. K. A pathobiont of the microbiota balances host colonization and intestinal inflammation. Cell. Host. Microbe 7, 265–276 (2010).
41. Young, V. B. & Schauer, D. B. Cytotoxic distending toxin: a bacterial toxin which disrupts the eukaryotic cell cycle. Chem. Rev. 113, 936–939 (2009).
42. Kuehl, C. J., Wood, H. D., Marsh, T. L., Schmidt, T. M. & Young, V. B. Colonization of the cecal mucosa by Helicobacter hepaticus impacts the diversity of the indigenous microbiota. Infect. Immun. 73, 6952–6961 (2005).
43. Whany, M. T. et al. Rapid onset of ulcerative typhlocolitis in B6.129P2-Il10tm1Cgn (IL-10/-) mice infected with Helicobacter hepaticus is associated with decreased colonization by altered Schaedler’s flora. Infect. Immun. 74, 6615 (2006).
44. Halmé, L., Rautelin, H., Leidenius, M. & Kosunen, T. U. Inverse correlation between Helicobacter pylori infection and inflammatory bowel disease. J. Clin. Pathol. 49, 65–67 (1996).
45. Pearce, C. B., Duncan, H. D., Timmis, L. & Green, J. R. Assessment of the prevalence of infection with Helicobacter pylori in patients with inflammatory bowel disease. Gastroenterology 118, 439–443 (2000).
Of Yu et al. 50. Parlak, E., Ulker, A., Ding, Y. Jin, X., Chen, Y. P., Chen, S. H. & Xiang, Z. Association between Helicobacter pylori infection and gastrointestinal lesions in patients with Crohn's disease. J. Gastroenterol. 36, 740–747 (2001).

Feeney, M. A. et al. A case-control study of childhood environmental risk factors for the development of inflammatory bowel disease. Eur. J. Gastroenterol. Hepatol. 14, 529–534 (2002).

Parlak, E., Ulker, A., Ding, Y. Jin, X., Chen, Y. P., Chen, S. H. & Xiang, Z. Association between Helicobacter pylori infection and gastrointestinal lesions in patients with Crohn's disease. J. Gastroenterol. 36, 740–747 (2001).

Pellicano, R. et al. Prevalence of Helicobacter pylori infection in patients with inflammatory bowel disease. Am. J. Gastroenterol. 96, 3510–3510 (2001).

Vare, P. O. et al. Seroprevalence of Helicobacter pylori infection in inflammatory bowel disease: a Helicobacter pylori infection a protective factor? Scand. J. Gastroenterol. 36, 1295–1300 (2001).

Matsumura, M. et al. Prevalence of Helicobacter pylori infection and correlation between severity of upper gastrointestinal lesions and Helicobacter pylori infection in Japanese patients with Crohn's disease. J. Gastroenterol. 36, 740–747 (2001).

Zhang, S. et al. Role of Helicobacter pylori infection in inflammatory bowel disease. Scand. J. Gastroenterol. 36, 87–88 (2001).

Próopor, L., Schandl, L., Oroz, Z., Magyar, P. & Tulaszy, Z. Lower prevalence of Helicobacter pylori infection in patients with inflammatory bowel disease but not with chronic obstructive pulmonary disease-antibiotic use in the history does not play a significant role. Helicobacter 9, 278–283 (2004).

Sładek, M. et al. The low prevalence of Helicobacter pylori gastritis in newly diagnosed inflammatory bowel disease children and adolescents. Pediatr. Lith. 64, 65–67 (2003).

Song, M. J. et al. [The prevalence of Helicobacter pylori infection in Korean patients with inflammatory bowel disease, a multicenter study]. Korean J. Gastroenterol. 36, 391–397 (2003).

Pang, Z., Li, M. F., Zhao, H., Zhou, C. L. & Shen, B. W. Low prevalence of Helicobacter pylori infection in Chinese Han patients with inflammatory bowel disease]. J. World J. Gastroenterol. 17, 3661–3665 (2009).

Xu, L. L., Wu, Y. S., Fan, L. J. & Tao, Z. Q. Correlation study between Helicobacter pylori and ulcerative colitis. Med. J. Mod. 38, 647–648 (2010).

Pellicano, R. et al. Prevalence of Helicobacter pylori infection in patients with inflammatory bowel disease: pilot study. Rev. Esp. Enferm. Dig. 102, 675–680 (2010).

Zhang, S. et al. Role of Helicobacter species in Chinese patients with inflammatory bowel disease. J. Clin. Microbiol. 49, 1987–1991 (2011).

Sonnenberg, A. & Genta, R. M. Low prevalence of Helicobacter pylori infection among patients with inflammatory bowel disease. Aliment. Pharmacol. Ther. 35, 469–476 (2012).

Xiang, Z. et al. Helicobacter pylori infection and Crohn’s disease: a retrospective single-center study from China. World J. Gastroenterol. 19, 4576–4581 (2013).

Jin, X., Chen, Y. P., Chen, S. H. & Xiang, Z. Association between Helicobacter pylori infection and ulcerative colitis—a case control study from China. Int. J. Med. Sci. 10, 1479–1484 (2013).

Xin, Y., Jiang, Y., Zhang, Z. G., Qi, F. X. & Li, M. Relationship between Helicobacter pylori infection and inflammatory bowel disease. Med. Inf. 11, 383–384 (2013).

Ali, A., Kazaka, C., Mossood, U., Alam, A. & Lakwar, G. Low prevalence of Helicobacter pylori infection in IBD patients from a predominantly African/ Caribbean urban center. Inflamm. Bowel Dis. 19, 555–566 (2013).

Roka, K. et al. The prevalence of Helicobacter pylori gastritis in newly diagnosed children with inflammatory bowel disease. Helicobacter 19, 400–405 (2014).

Ma T. H., Yang X., Xie R. H., Yan W. Clinical analysis of Helicobacter pylori infection in ulcerative colitis patients[J]. J. Shanxi Med. Univ. 47(1), 68–70 (2016).

Shi, T. T., Zhu, L. & Wang, Y. D. Helicobacter pylori infection in patients with inflammatory bowel diseases. China J. Med. Mod. 27, 101–103 (2017).

Zhou, L. Y. et al. Relationship between Helicobacter pylori infection and ulcerative colitis. Chin. J. Clin. Res. 40, 447–450 (2017).

Luther, J., Davis, C. & Higgins, P. D. & Kao, J. Y. Association between Helicobacter pylori infection and inflammatory bowel disease: a meta-analysis and systematic review of the literature. Inflamm. Bowel Dis. 16, 1077–1084 (2010).

Rokkas, T., Griebert, J. P., Nov, Y. & O'Moran, C. The association between Helicobacter pylori infection and inflammatory bowel disease based on meta-analysis. United European Gastroenterology. Journal 3, 539–550 (2015).

Wu, X. W., Ji, H. Z., Yang, M. F., Wu, L. & Wang, Y. F. Helicobacter pylori infection and inflammatory bowel disease in Asians: a meta-analysis. World J. Gastroenterol. 21, 4750–4756 (2015).
66. Klingenberg, R. 1 et al. Depletion of FOXP3+regulatory T cells promotes hypercholesterolemia and atherosclerosis. J. Clin. Investig. 123, 1323–1334 (2013).

67. Kim, J. et al. Cutting edge: depletion of FOXP3+cells leads to induction of autoimmunity by specific ablation of regulatory T cells in genetically targeted mice. J. Immunol. 183, 7631 (2009).

68. Du, Y., Chen, X., Lin, X.-O., Wu, W. & Huang, Z. M. Tumor-derived CD4+CD25+Tregs inhibit the maturation and antigen-presenting function of dendritic cells. Asian Pac. J. Cancer Prev. 16, 2665–2669 (2015).

69. Saiy, A. et al. TLR2-activated B cells suppress Helicobacter-induced pre-neoplastic gastric immunopathology by inducing T regulatory-1 cells. J. Immunol. 186, 878–890 (2011).

70. Lundgren, A. et al. Mucosal FOXP3-expressing CD4+CD25high regulatory T cells in Helicobacter pylori-infected patients. Infect. Immun. 73, 523–531 (2005).

71. Arnold, I. C. et al. Helicobacter pylori infection prevents allergic asthma in mouse models through the induction of regulatory T cell. J. Clin. Investig. 121, 3088–3093 (2011).

72. Driel, I. R. V. & Ang, D. K. Role of regulatory T cells in gastrointestinal inflammatory disease. J. Gastroenterol. Hepatol. 23, 171–177 (2008).

73. Izuoe, A., Coombes, J. L. & Powrie, F. Regulatory T cells suppress systemic and mucosal immune activation to control intestinal inflammation. Immunol. Rev. 212, 256–271 (2008).

74. Mottet, C., Uhlig, H. H. & Powrie, F. Cutting edge: cure of colitis by CD4+CD25+regulatory T cells. J. Immunol. 170, 3939–3943 (2003).

75. Luther, J. et al. Helicobacter pylori DNA decreases proinflammatory cytokine production by dendritic cells and attenuates dextran sulphate sodium-induced colitis. Gut 60, 1479 (2011).

76. Onishi, Y., Feher, V., Yamaguchi, T. & Sakaguchi, S. Foxp3+natural regulatory T cells preferentially form aggregates on dendritic cells in vitro and actively inhibit their maturation. Proc. Natl Acad. Sci. USA 105, 11013–11018 (2008).

77. Leach, M. W., Davidson, N. J., Fort, M. M., Powrie, F. & Rennick, D. M. The role of the IL-10 in inflammatory bowel disease: “of mice and men.” Toxicol. Pathol. 27, 123–133 (1999).

78. Ohshuka, Y. & Sanderson, I. R. Transforming growth factor-beta: an important cytokine in the mucosal immune response. Curr. Opin. Gastroenterol. 16, 541–545 (2000).

79. Zou, L. et al. The association between three promoter polymorphisms of IL-10 and inflammatory bowel disease (IBD): a meta-analysis. Autoimmunity 47, 27–39 (2014).

80. Beuge, B. et al. Defective IL-10 signaling defining a subgroup of patients with inflammatory bowel disease. Am. J. Gastroenterol. 106, 1544 (2011).

81. Yao, X. C., Wang J. Expression level of TREG, TGF-β and IL-10 in IBD patients and their clinical value. J. Shandong Med. Coll. 39, 107–110 (2017).

82. Powrie, F., Carlin, J., Leach, M. W., Mauze, S. & Coffman, R. L. A critical role for transforming growth factor-β but not interleukin 4 in the suppression of T helper type 1-mediated colitis by CD45RB low CD4+ T cells. J. Exp. Med. 183, 2659–2674 (1996).

83. Neurath, M. F. et al. Experimental granulomatous colitis in mice is abrogated by induction of TGF-β-mediated oral tolerance. J. Exp. Med. 183, 2659–2674 (1996).