Immune response modulation in inflammatory bowel diseases by *Helicobacter pylori* infection

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Abstract

Many studies point to an association between *Helicobacter pylori* (*H. pylori*) infection and inflammatory bowel diseases (IBD). Although controversial, this association indicates that the presence of the bacterium somehow affects the course of IBD. It appears that *H. pylori* infection influences IBD through changes in the diversity of the gut microbiota, and hence in local chemical characteristics, and alteration in the pattern of gut immune response. The gut immune response appears to be modulated by *H. pylori* infection towards a less aggressive inflammatory response and the establishment of a targeted response to tissue repair. Therefore, a T helper 2 (Th2)/macrophage M2 response is stimulated, while the Th1/macrophage M1 response is suppressed. The immunomodulation appears to be associated with intrinsic factors of the bacteria, such as virulence factors - such oncogenic protein cytotoxin-associated antigen A, proteins such *H. pylori* neutrophil-activating protein, but also with microenvironmental changes that favor permanence of *H. pylori* in the stomach. These changes include the increase of gastric mucosal pH by urease activity, and suppression of the stomach immune response promoted by evasion mechanisms of the bacterium. Furthermore, there is a causal relationship between *H. pylori* infection and components of the innate immunity such as the NLR family pyrin domain containing 3 inflammasome that

directs IBD toward a better prognosis.

Key Words: Cytotoxin-associated antigen A oncoprotein; Gut microbiota; *Helicobacter pylori*; *Helicobacter pylori* neutrophil-activating protein; Immunological modulation; Inflammatory bowel disease; NLR family pyrin domain containing 3 inflammasome

Core Tip: *Helicobacter pylori* (*H. pylori*) infection seems to modulate the immune response triggered by inflammatory bowel disease in a way that makes it less aggressive. The virulence factors of *H. pylori*, as well as the mechanisms that allow it to remain in the stomach environment, appear to change the intestinal microenvironment and modulate the local immune response, contributing to a disease with milder symptoms and less tissue damage.

INTRODUCTION

Inflammatory bowel diseases (IBD) are a group of chronic conditions affecting the gastrointestinal tract, characterized by episodes of abdominal pain, diarrhea, bloody stools, and weight loss. The two main types of IBD are Crohn's disease (CD) and ulcerative colitis (UC)[1]. In CD any area of the gastrointestinal tract can be affected, but the most affected regions are the terminal ileum, the cecum, the perianal region, and the colon, while in UC the inflammation is restricted to the colon and rectum[1]. Regarding histology, in CD the intestine presents thickened submucosa, transmural inflammation, ulceration and non-caseating granulomas, while in UC the inflammation is limited to the mucosa, with crypts and abscesses[2].

The pathogenesis of IBD is complex and involves a combination of genetic, environmental, and immunological factors. The gut microbiota is critical to homeostasis in this organ and contributes to the tolerance process, to the development and differentiation of the local and systemic immune system, and may protect the host from pathogenic enteric infections. However, in IBD, luminal bacteria trigger deregulated immune responses, acting as the main environmental factor for the development of these pathologies[3,4].

The loss of tolerance to the commensal microbiota seems to be related to the genetic susceptibility of the individual and to an imbalance in the composition of the microbiota[5]. IBD patients have changes in stool composition, with less bacterial quantity and diversity[6,7].

Genome wide association studies of IBD have identified 99 non-overlapping genetic risk loci including 28 that are shared between CD and UC[8]. These genetic alterations seem to implicate several important pathways, such as intestinal barrier function, regulation of innate and adaptive immunity, reactive oxygen species formation, autophagy, and endoplasmic reticulum stress[9]; associations were identified between polymorphisms in the genes for interleukin (IL)-10, IL-10 receptor alpha, and components of this signaling pathway - signal transducer and activator of transcription 3, tyrosine kinase 2, and JAK2, with the early development of IBD[10].

Dysregulation of the immune component in IBD is marked by abnormal mucus production, failure to repair the epithelial barrier, and excessive and persistent activation of T lymphocytes, B cells, dendritic cells, macrophages, and natural killer cells[11,12].

Naive TCD4+ cells can differentiate into T helper 1 (Th1), Th2, Th9, Th17 and regulatory T (Treg) subpopulations; the main stimulus for differentiation into Th1 cells - secreting interferon (IFN)-γ, tumor necrosis factor (TNF) and IL-2, is the expression of IL-12, while IL-4 leads to differentiation into Th2 cells, whose cytokine pattern is marked by the expression of IL-4, IL-5, IL-13 and IL-25[13]. Classically, CD and UC are described as diseases with a Th1 and Th2 immune pattern, respectively[14-16], since typically CD patients have higher IFN-γ and IL-2 expression than UC patients[17,18], that express more IL-5 and IL-13[19,20]. However, some studies contradict this information, since lower levels of IL-13 were seen in UC patients compared to CD patients[21], and high levels of IFN-γ were found in carriers of both diseases[22]. In line with this, Bernardo *et al*[23] found a mixed cytokine pattern in biopsies from UC patients, associated with low IL-13 levels.

A Th17 pattern response prevails in the gut. The differentiation into Th17 cells leads to the expression of IL-17, IL-21, IL-22, and IL-23, which are found in large quantities in the intestine of IBD patients[24]. A study using IL-17 receptor (IL-17R) knockout mice showed that IL-17R deficiency protected the animals from developing trinitrobenzene sulfonic acid (TNBS)-induced colitis[25-27].

Although not conclusive, there is evidence to indicate that two members of this cytokine family have different effects; IL-17A appears to have a protective effect through inhibition of the Th1 response[28], furthermore, other studies indicate that deficiency of this cytokine causes exacerbation of colitis, while IL-17F contributes to and aggravates the inflammatory process[29]. Despite the prevalence of Th17 cells in the gut in the absence of IBD, this response pattern appears to be exacerbated with disease onset leading to increased production of pattern marker cytokines. Perhaps this increase occurs relatively disproportionately, prioritizing the increase in cytokines that induce an inflammatory response, such as IL-17F.

Treg cells which is characterized by constitutive expression of forkhead/winged helix transcriptional factor P3 (FoxP3), CD25 and cytotoxic T lymphocyte-associated protein 4, play a major role in the pathogenesis of IBD[30]. In these diseases, there is a significant dysfunction in the activity of these cells, either by being in low numbers or by having their function suppressed. It has been observed that effector cells from IBD patients exhibit relative resistance to Treg-mediated suppression by expressing high levels of Smad7, an inhibitor of the transforming growth factor (TGF)-β signaling pathway[31,32]. The unbalanced and uncontrolled local immune response against the bacterial microbiota in the IBD occurs when it is poorly controlled by endogenous counter regulatory mechanisms, such as the immunosuppressive cytokine TGF-β. Studies show that the inefficiency in control occurs due to a blockade of TGF-β signaling, caused by a blockade in the phosphorylation of the signaling molecule associated with the TGF-β activated receptor, Smad3. The blockade of Smad3 activity is caused by the upregulation of the Smad7[33].

Individuals with a mutation in the *FOXP3* gene often suffer from intestinal inflammation[34]. Treg cells are able to convert to Th17 cells under inflammatory conditions, and the cytokine IL-1β is key in this process[35]. The balance between the Th17 and Treg response is important, especially in places such as the gut, where there is a commensal microbiota, to prevent deregulated immune responses. IBD patients have a reduced Treg/Th17 ratio in peripheral blood compared to healthy individuals. The installation of the inflammatory process in IBD seems to be fueled by an unbalanced increase in the production of Th17 cytokines, which promote the Th1 pattern. Pro-inflammatory cytokines produced by Th1 cells, such as IL-1β, potentiate the inflammatory process by decreasing the Treg/Th17 ratio, both by proportionally increasing the Th17 response and by reducing the suppression of the inflammatory response by Treg cells. Regarding Th9 cells - capable of exacerbating inflammatory processes by increasing epithelial permeability[36], are at high levels in CD and UC[37,38].

IMMUNOMODULATION OF THE INFLAMMATORY PROCESS AND PATHOGENESIS OF IBD BY *HELICOBACTER PYLORI*

Influence of Helicobacter pylori cytotoxin-associated antigen A+ infection on IBD prognosis

Cytotoxin-associated antigen A (*CagA*) is a gene found in the final portion of the Cag pathogenicity island of the *Helicobacter pylori* (*H. pylori*) genome and encodes the oncogenic protein CagA. Its presence is more frequent in East Asian populations than in those from the West, and determines a number of interactions between the bacterium and the host [39]. Although there is a causal relationship between *H. pylori* CagA+ and the incidence of cancers of the gastrointestinal tract[39,40], when it comes to IBD, especially CD and UC, the presence of the *CagA* gene may positively influence the prognosis of patients[41].

In a first analysis, age, genetic and environmental factors associated with innate and adaptive immunity are key factors in the development of IBD[42,43], thus the presence of *H. pylori* infection becomes yet another variable. Some studies point to several hypotheses for the improved prognosis of IBD in the presence of the *H. pylori CagA* gene, such as the conversion of the M1 macrophage lineage into M2 through modulation of the Th17/Treg immune response, in which there is a decrease in the levels of IL-17F and IL-21 with concomitant increase in the expression of IL-10 and Treg cells[44] due to increased plasma IL-13[45].

Also contributing to the process are increased anti-inflammatory responses through increased expression of CD163 and IL-10, suppression of toll like receptors (TLR) mediated signaling pathways[46], and control of the immune response through activation of pathways mediated by the basic leucine zipper transcription factor ATF-like 2 (BATF2)[47-49] (Figure 1).

The CD163 is a macrophage/monocyte scavenger receptor whose expression is positively regulated by IL-10. The upregulated expression of this receptor is one of the most marked changes in the M2/M1 phenotype switch; therefore, high expression of CD163 is characteristic in inflammatory processes[50,51]. According to studies, the number of CD163-M1 monocytes, as well as CD163+ and CD163+/IL-10+ M2 monocytes are significantly increased in individuals infected with *H. pylori*, in addition to having higher levels of IL-10. IL-10 production is significantly higher by M2 cells from individuals with *H. pylori* infection. In addition, individuals infected with CagA-positive *H. pylori* strains had a significantly higher number of CD163+ and CD163+/IL-10+ monocytes compared to those infected with CagA-negative strains[52].

The TLRs are expressed by cells of the intestinal epithelium, and by cells of the immune system present in the gut, such as leukocytes, dendritic cells, and various polymorphisms of these receptors have been associated with susceptibility to IBD[53,54] and they are involved in signaling pathways leading to the expression of several inflammatory genes[55,56]. BATF2 has unique functions in the regulation of cytokine gene expression by TLR signaling in macrophages[57].

H. pylori has metabolic adaptations for gastric colonization that, in the background, participate in modulating the inflammatory process of IBD. The urease enzyme that confers *H. pylori* resistance to stomach acidity, participates in immunomodulation as it alters particle opsonization, facilitates apoptosis, and by being presented by MHC II increases the expression of pro-inflammatory cytokines[58].
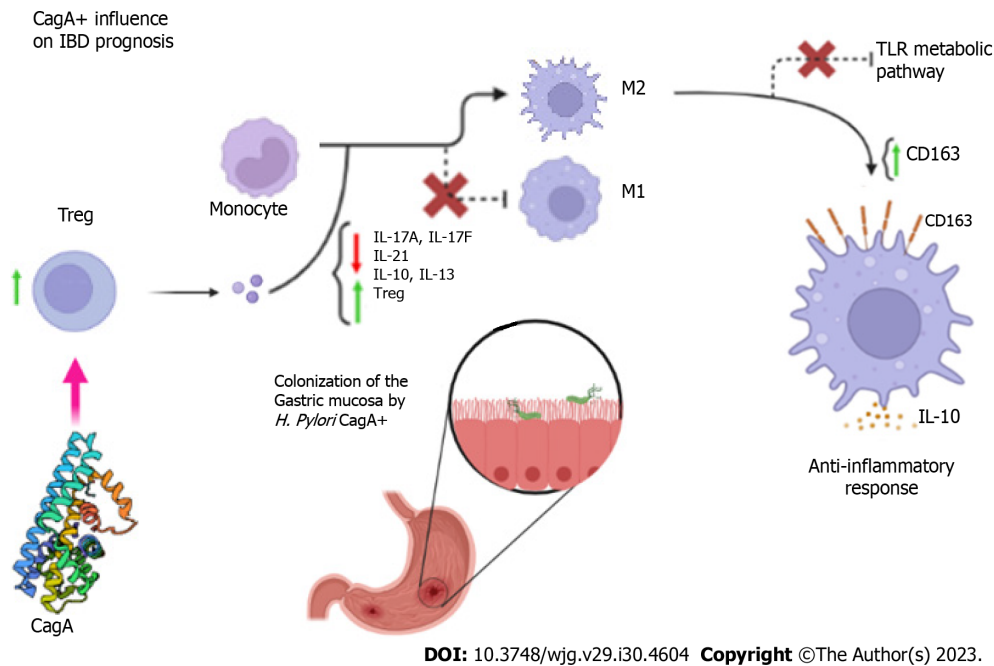
Figure 1 Mechanisms of *Helicobacter pylori* cytotoxin-associated antigen A+ on favorable prognosis of inflammatory bowel diseases. The presence of the cytotoxin-associated antigen A gene at the Cag pathogenicity island induces the modulation of T helper 17/Treg immunological response (1), which reduces levels of interleukin (IL)-17F, IL-17A, and IL-21 and increases the expression of IL-13, IL-10, and Treg (2). These two factors are synergists in the conversion process of the M1 to M2 macrophage lineage (3). Then, M2 macrophages suppress signaling mediated by toll-like receptors (4) and activate metabolic pathways mediated by basic leucine zipper transcription factor ATF-like 2, increasing CD163, a macrophage/monocyte scavenger receptor (5). Finally, the levels of IL-10 expression also increase (6), leading to anti-inflammatory effects (7) and, therefore, to a better prognosis on inflammatory bowel diseases. *H. pylori*: *Helicobacter pylori*; IL: Interleukin; TLR: Toll-like receptor; IBD: Inflammatory bowel disease; CagA: Cytotoxin-associated antigen A; Treg: Regulatory T.

The flagella of *H. pylori*, besides the fundamental importance in its motility for gastric colonization, also induces an inflammatory response. FlaA and FlaB flagellins can promote a humoral response by stimulating the production of specific antibodies[59,60]. Furthermore, studies report that bacteria with increased motility increase IL-8 release and suggest that genes which regulate flagellin production may alter adhesin expression[61-63] facilitating colonization. The chemoattractant effect of IL-8 is all too well known, however, data on the association of IL-8 with *H. pylori* infection are still scarce[64].

Superoxide dismutase from *H. pylori* has also been shown to have a potential immune suppressive effect by inhibiting the production of pro-inflammatory cytokines, through inhibition of pathways activated by the transcription factor nuclear factor kappa B (NF-κB), as well as macrophage inflammatory protein 1-α[65].

Modification of bacterial gut microbiota by H. pylori

The alteration in the pattern of gastric secretion by *H. pylori* is closely related to the modification of the microbiota of the gastrointestinal tract[66]. Hypochlorhydria enables colonization of the distal intestine by acidic pH-sensitive bacteria; this causes people infected with *H. pylori* to have a more diverse alpha intestinal microbiota compared to uninfected people [66-68]. These changes reflect higher percentages of acidophilic bacteria, proteobacteria, bacteria of the genera *Lactobacillus*, *Haemophilus*, *Streptococcus* and *Gemella*; in contrast, there is a decrease in the percentage of pathogenic anaerobic bacteria such as *Clostridium*[69-72].

In addition to the variation in intestinal pH being one of the factors that alter the diversity of the gut bacterial microbiota, it can also be influenced by the virulence factors CagA and VacA of *H. pylori*, which alter the immune response of the infected individual[73-75]. Hormonal factors, influenced by *H. pylori* infection such as an increase of gastrin secretion alter gut metabolism, in addition, leptin has been directly related to an increase of the amount of the probiotic bacteria *Bifidobacterium* and *Lactobacillus*[76].

Indeed, there is an altered composition of the local microbiota of IBD patients[77]. In these diseases an exacerbated immune response against the commensal microbiota occurs in genetically predisposed individuals and, studies suggest that the balance between pathogenic and beneficial bacterial species is altered in these ones[78]. Therefore, the dysbiosis promoted by *H. pylori* infection may help explain the inverse relationship between bacterial infection and IBD in individuals with the two conditions concomitantly, although the underlying molecular mechanisms are not fully understood[79].

CO-IMMUNOMODULATION OF IBD BY NLR FAMILY PYRIN DOMAIN CONTAINING 3 INFLAMMASOME AND *H. PYLORI* INFECTION

The NLR family pyrin domain containing 3 (NLRP3) inflammasome is a multiprotein complex that plays a crucial role in the innate immune response. The complex is formed by the NLRP3 receptor, the adaptor protein caspase-recruitment domain (ASC) and the enzyme caspase-1 and, appears to play a role in the negative association between IBD and *H. pylori* infection by the IL-1β and IL-18 activity. NLRP3 recognizes a wide variety of stimuli linked to pathogen-associated molecular patterns and damage-associated molecular patterns through pattern recognition receptors such as TLRs and nucleotide-binding oligomerization domain 2. Activation of NLRP3 includes a priming process which components are expressed in greater quantities and depends on several upstream signals such as potassium and chloride efflux, calcium mobilization, lysosomal disruption, and mitochondrial dysfunction with increased reactive oxygen species[80].

Activation of the inflammasome culminates i4n expression of NF-κB and cleavage/activation of caspase-1, responsible for processing pro-IL-1β and pro-IL-18, which are cleaved into their active forms[81,82]. Furthermore, activation of NLRP3 leads to proptosis, a form of programmed cell death mediated by gasdermin D protein. Caspase-1 cleaves gasdermin D, removing its carboxy-terminal portion, which allows its insertion and polymerization into the plasma membrane forming pores. Proptosis also appears to induce the secretion of IL-1β and IL-18[83].

Caspase-1 is highly expressed in the mucosa of the patients infected with *H. pylori*. However, it is observed that together, IL-1β and IL-18 seem to play different roles in controlling the infection and the pathogenicity of the bacterium. While IL-1β presents itself as a potent pro-inflammatory agent, IL-18 has regulatory properties and controls responses mediated by TCD4+ cells. Studies have shown that mice that failed to process IL-18 in the absence of caspase-1 had less bacterial colonization, more robust Th17 responses, and more evident immune pathogenicity compared to control animals[84]. Furthermore, mesenchymal stem cells stimulated by this cytokine promote differentiation of Treg cells into virgin TCD4+ cells, limiting the Th17 response[85], promoting a tolerogenic activity and adjusting chronic inflammation in the gastric mucosa (Figure 2).

The absence of caspase-1 results in an inefficient protective immune response, with a less pronounced Th1 and Th17 pattern[86,87]. There is strong evidence of an association between IL-18 and the prevention and control of allergic diseases such as asthma and rhinitis, through pulmonary infiltration of large amounts of Treg and tolerogenic dendritic cells. This association seems especially beneficial in relation to infection with *H. pylori* CagA+ strains, as observed in a study wherein mice infected with the bacteria in the neonatal period developed specific immunological tolerance and protection against gastric immunopathology resulting from *H. pylori* CagA+ infection[88].

Studies with animal models have shown that NLRP3 activation induced by *H. pylori* infection appears to improve the prognosis of IBD. Engler *et al*[89] observed that mice exposed to the bacterium developed less severe forms of dextran sulfate sodium (DSS)-induced colitis, with significantly milder inflammation and epithelial changes. These positive effects were also observed in animals treated with *H. pylori* extracts. Such beneficial effects are accompanied by positive regulation of TGF-β and the transcription factor caudal-related homeobox transcription factor 2, which regulates the expression of mucins such as mucin 2, a fact that was associated with signaling by NLRP3 and IL-18 production by caspase-1.

Zaki *et al*[90] demonstrated that NLRP3 -/- or ASC -/- mice are more susceptible to DSS-induced colitis and caspase-1 -/- mice are more susceptible to weight loss, diarrhea, rectal bleeding and mortality during the chronic and acute phases of DSS- or TNBS-induced colitis. These findings are related to IL-18 production and its mucosal barrier repair function. Furthermore, IL-18 -/- and IL-18R -/- mice exhibit greater susceptibility to DSS-induced colitis, associated with higher mortality and more severe histopathological changes[91]. Previous studies have reported that the absence of the adaptor protein myeloid differentiation primary response 88 (MyD88), which is involved in the production of IL-18 and IL-1β, increases the severity of inflammatory disease, indicating the importance of MyD88-dependent signaling pathways, such as the TLR4-MyD88 pathway, in blocking the onset and progression of IBD[92-94]. MyD88 is the main signaling adaptor protein of the TLR family. Studies using MyD88-deficient mice suggest a dominant role for TLR/MyD88 signal transduction in preventing intestinal inflammation after acute epithelial injury by promoting epithelial repair[94,95].

Yao *et al*[96] conducted a study with NLRP3R258W mutant mice, a mutation homologous to NLRP3R260W in humans, which causes increased inflammasome activity. The mutant mice developed DSS-induced colitis with milder symptoms compared to wild-type animals, in addition to lower expression of inflammatory mediators, higher expression of IL-18 and IL-1β, and fewer colon tumors. These positive effects were associated with higher activity of Treg cells, positively regulated by IL-1β and fundamental in controlling inflammation. In this study no evidence was found that directly points to IL-18 as an effector molecule in the activation of the inflammasome, but it is believed that this cytokine may be indirectly affected by NLRP3 through secondary effects. However, IL-18 deficiency was shown to override the protective effect of the NLRP3R258W mutation.

IMMUNOMODULATION OF IBD BY NEUTROPHIL-ACTIVATING PROTEIN OF *H. PYLORI*

H. pylori neutrophil-activating protein (HP-NAP) is a virulence factor that plays an important role in immunomodulation. HP-NAP refers to *H. pylori* mini-ferritin, a protein with the ability to activate the production of oxygen radicals by neutrophils promoting their adhesion to the vascular endothelium[97]. Neutrophil adhesion occurs by the positive regulation of β-2-integrin (CD18) expression in a high-affinity state[98,99].
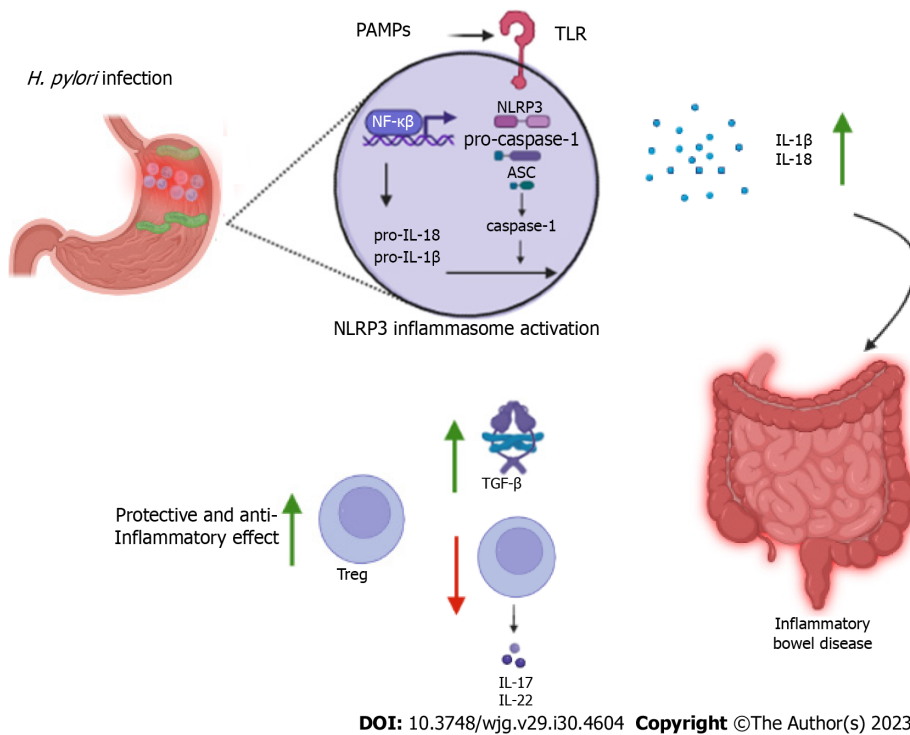
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Figure 2 Immunomodulation of the NLR family pyrin domain containing 3 inflammasome and protection against inflammatory bowel diseases. Pathogen-associated molecular patterns from *Helicobacter pylori* are recognized by the NLR family pyrin domain containing 3 (NLRP3) inflammasome toll-like receptors leading to responses that appear to be associated with improved prognosis and an anti-inflammatory effect. Activated NLRP3 is able to increase the expression of caspase-1 which activates the cytokines interleukin (IL)-18 and IL-1β. The positive regulation of these cytokines leads to extragastric immunomodulation by suppressing the T helper 17 subpopulation and increasing regulatory T, transforming growth factor-β and mucins. *H. pylori*: *Helicobacter pylori*; IL: Interleukin; PAMPs: Pathogen-associated molecular patterns; TLR: Toll-like receptor; TGF: Transforming growth factor; NLRP3: NLR family pyrin domain containing 3; Treg: Regulatory T.

The mini-ferritins have the ability to influence host immune cells in addition to protecting bacterial DNA from oxidizing radicals[100]. HP-NAP is released by *H. pylori* near the gastric epithelial monolayer, thus activating macrophages/monocytes and mast cells, with the release of pro-inflammatory cytokines TNF-α, IL-6, IL-12 and IL-23[101, 102]. Similar to the chemokine CXCL8, HP-NAP directly promotes leukocyte recruitment; after HP-NAP transcytosis by endothelial cells, part of these proteins remain bound to the luminal portion of the endothelium, increasing the expression of β-2-integrin and changing the local spatial conformation, a fact that culminates in the extravasation of immune cells[99, 103].

The IL-8 secretion by neutrophils present at the site of inflammation enables the recruitment of more neutrophils and other immune cells. IL-8 secretion is promoted by HP-NAP and mediated through interactions with TLR2 receptors and pertussis toxin-sensitive G proteins[104]. HP-NAP also induces mast cells and basophils to secrete TNF-α, IL-6, IL-8, IL-12 and IL-23, and stimulates mast cells to release histamine and IL-6[101,102,105]. Besides influencing innate immunity, HP-NAP modulates adaptive immunity by promoting the release of IL-12 and IL-23 by neutrophils and monocytes, thereby causing a Th1 polarization, and directing the maturation of monocytes to mature dendritic cells[102].

The mature dendritic cells are stimulated by HP-NAP to express MHCII and release Th1 pattern cytokines such as IL-12[102,106]. The increased secretion of IL-12 in the gastrointestinal microenvironment, promoted by HP-NAP, causes gastric specific T lymphocyte subpopulations to be able to produce large amounts of IFN-γ and TNF-α and, to exhibit cytotoxic activity[102]. Increased Th1 pattern and cytotoxic response, induced by *H. pylori* infection, may be beneficial in pathologies which the Th2 response is the detrimental mechanism (Figure 3). The ability of HP-NAP to reduce Th2 activity due to the polarization towards Th1 was proven in experiments using mice with atopic dermatitis[107]. Therefore, HP-NAP may have a therapeutic effect in situations which there is a predominance of Th2 response, as was observed in HP-NAP inoculation assays in mice with allergic asthma, which significantly reduced serum immuno-globulin E levels with concomitant increase in IL-2, thus decreasing eosinophil infiltration[108].

Thus, the Th1-directed polarization promoted by HP-NAP, may be a possible explanation for the improvement of IBD symptoms, whose pathogenesis may be the result of a dysregulated Th2 response, as occurs in UC, in which there is a predominance of a Th2 response and inhibition of the Th1 response, in individuals infected with *H. pylori*[109-112].

CONCLUSION

Although significant progress has been made over the last few years in defining the mechanisms that *H. pylori* use to influence on IBD evolution, there is clearly much that remains to be elucidated and many questions persist. In this review

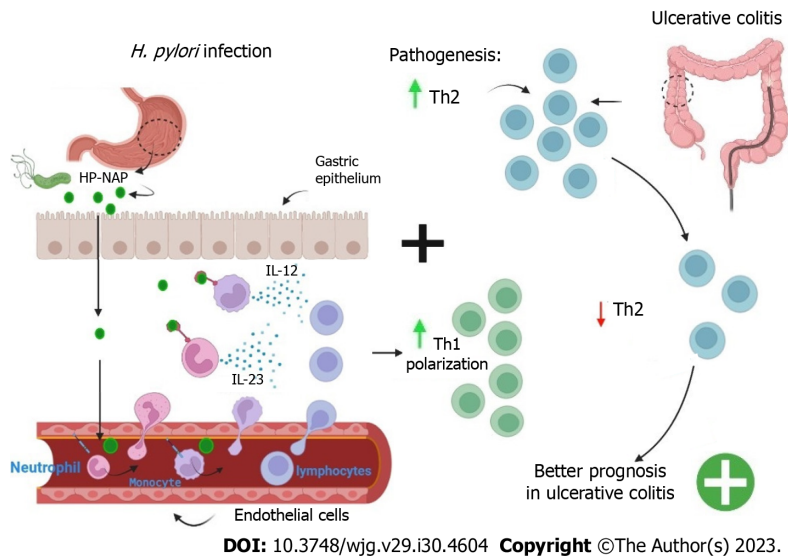**DOI:** 10.3748/wjg.v29.i30.4604 **Copyright** ©The Author(s) 2023.

Figure 3 Hypothesis on correlation between concomitant infection with *Helicobacter pylori* and the presence of ulcerative colitis (inflammatory bowel disease), which has a pathological pattern of exacerbated T helper 2 response. The schematic shows HP-NAP being secreted into the gastric mucosa by *Helicobacter pylori* (*H. pylori*). Then, HP-NAP undergoes a process of transcytosis by endothelial cells, binding to the luminal side of the blood vessel. With this, there is an alteration in the expression of β-2-integrin, with the recruitment of neutrophils and monocytes, which carry out diapedesis. The recruited leukocytes secrete cytokines [interleukin (IL)-12 and IL-23], which promote a polarization of the circulating lymphocytes to a T helper 1 (Th1) pattern. The Th1 polarization causes a reduction in the Th2 response, this could explain the improvement of ulcerative colitis symptoms in patients infected with *H. pylori*. *H. pylori*: *Helicobacter pylori*; IL: Interleukin; Th: T helper; HP-NAP: *Helicobacter pylori* neutrophil-activating protein.

we emphasize the role of *H. pylori* CagA+ and HP-NAP on favorable prognosis of IBD. The pathogenesis of IBD is complex and involves a combination of genetic, environmental, and immunological factors. Classically, CD and UC are described as diseases with a Th1 and Th2 immune pattern, but the prevalence of type response remains under study.

Regarding the cellular pattern, Th17 cells have been demonstrated at the site of inflammation, but the levels of total cytokine markers of these patterns remain variable on models' diversity. Treg cells play a major role in the pathogenesis of IBD by suppression of Smad3 and consequently overexpression Smad7, an inhibitor of the TGF-β signaling pathway. Moreover, Th9 cells - capable of exacerbating inflammatory processes by increasing epithelial permeability, are at high levels in CD and UC.

In summary, targeting NLRP3 inflammasome by *H. pylori* infection allows the exacerbation of IL-1β and IL-18 that culminates in high levels of TGF-β and low levels of IL-17 and IL-22 on IBD. The patients with *CagA* gene can induce the Treg cells which contributes to the polarization of the M1 macrophage into M2 macrophage lineage through concomitant increase of the expression of IL-10 and more Treg cells. At the same time, HP-NAP has an important role in immunomodulation by reactive oxygen species production neutrophil-induced. The ability of HP-NAP to reduce Th2 activity due to the polarization towards Th1 response may be a possible explanation for the improvement of IBD symptoms, in which there is a predominance of a Th2 response and inhibition of the Th1 response like occurs in individuals infected with *H. pylori*.

Regarding the capacity of CagA+ and HP-NAP to control inflammation and autoimmunity, and their implication in preventing IBD evolution, it seems probable that a clear understanding of how CagA+ and HP-NAP work on Treg cells, cytokines and macrophages-induced will present definitive opportunities for therapeutic intervention.

FOOTNOTES

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