REVIEW

Systems-wide analyses of mucosal immune responses to *Helicobacter pylori* at the interface between pathogenicity and symbiosis

Barbara Kronsteiner*a, Josep Bassaganya-Riera*a, Casandra Philipson*b, Monica Viladomiu*a, Adria Carbob, Vida Abedia, and Raquel Hontecillas*a

aNutritional Immunology and Molecular Medicine Laboratory and Center for Modeling Immunity to Enteric Pathogens; Virginia Bioinformatics Institute; Virginia Tech; Blacksburg, VA USA; bBioTherapeutics; Blacksburg, VA USA

ABSTRACT

*Helicobacter pylori* is the dominant member of the gastric microbiota in over half of the human population of which 5–15% develop gastritis or gastric malignancies. Immune responses to *H. pylori* are characterized by mixed T helper cell, cytotoxic T cell and NK cell responses. The presence of Tregs is essential for the control of gastritis and together with regulatory CX3CR1+ mononuclear phagocytes and immune-evasion strategies they enable life-long persistence of *H. pylori*. This *H. pylori*-induced regulatory environment might contribute to its cross-protective effect in inflammatory bowel disease and obesity. Here we review host-microbe interactions, the development of pro- and anti-inflammatory immune responses and how the latter contribute to *H. pylori*’s role as beneficial member of the gut microbiota. Furthermore, we present the integration of existing and new data into a computational/mathematical model and its use for the investigation of immunological mechanisms underlying initiation, progression and outcomes of *H. pylori* infection.

KEYWORDS

bacterial pathogenesis, commensal; helicobacter pylori; host tolerance; IFN-γ; immune evasion; information biology; treg

Introduction

*H. pylori* is a Gram-negative, microaerophilic bacterium within the class of Epsilonproteobacteria. It chronically colonizes the human gastric microenvironment and is one of the most genetically diverse bacterial species that has colonized the stomach since early in human evolution.1,2 The study of *H. pylori* populations such as hpAfrica, hpEurope, hspEAsia, and hspAmerind3 has delineated competition between strains and suggests co-adaptation and co-evolution with its host that parallels human migration throughout the globe.

Since its initial discovery by Marshall and Warren,4 *H. pylori* has been associated with the development of chronic gastritis, peptic ulcer disease, gastric adenocarcinoma, and gastric mucosa-associated lymphoid tissue (MALT) lymphoma.5,6 Although it is present in the stomach of over 50% of the human population worldwide, only 15% develop serious gastric and duodenal pathologies. Mounting clinical and epidemiological evidence suggests that the presence of *H. pylori* can protect from the development of various diseases including esophageal and cardiac pathologies,7-10 childhood asthma and allergies.11-14 Originally viewed solely as a pathogen, recent studies are unveiling commensal and symbiotic roles for *H. pylori* as the predominant member of the human gastric microbiota.15 Therefore, investigating the complex tolerance mechanisms that facilitate the co-existence between *H. pylori* and its human host may yield a deeper understanding of mechanisms of immunoregulation at the mucosal sites. This is a first step toward predicting pathogenic versus beneficial health outcomes of host-*H. pylori* interactions.

The life-long persistence of *H. pylori* in the human stomach suggests that the host response fails to clear the infection and induces an underlying regulatory response. Indeed, *H. pylori* induces a mixed immune response characterized by T helper (Th) 1, Th17 and regulatory T cell (Treg) responses. Whether *H. pylori* exerts a protective effect in the context of a dysregulated immune response or whether it contributes to cell damage and malignant transformation is dependent on host-microbial interactions.

This review sheds new light on the complex interactions of host- and microbial-factors in immune
responses to \textit{H. pylori} specifically emphasizing the role of inflammasome and TLR signaling in shaping the innate and adaptive T cell responses. We will further discuss novel mechanistic insights leading to \textit{H. pylori}-induced gastritis and mechanisms of immune evasion by \textit{H. pylori} and how this might help explain the role of \textit{H. pylori} as an amphibiont at the interface between commensalism/symbiosis and pathogenicity. Furthermore, we will discuss the use of novel computational modeling approaches to systematically integrate existing knowledge and varied datasets into information processing representations of the mucosal immune system. These computational approaches have facilitated characterizing emerging behaviors and improving our systems-wide understanding of the mechanisms of host-\textit{H. pylori} interactions implicated in the initiation, progression and health outcomes of infection.

\textbf{\textit{H. pylori} and its human host: An intimate relationship}

\textit{H. pylori} can persist in the human stomach for a lifetime.\textsuperscript{16} Its ability to survive in the gastric niche is tightly connected to the expression of various pathogenicity factors that enable adherence and penetration of the epithelial cell layer and manipulation of innate and adaptive immune responses at the gastric mucosa. Dozens of bacterial factors are involved in \textit{H. pylori}-mediated colonization and molecular pathogenesis including adhesins, outer membrane proteins,\textsuperscript{17} urease, catalase, neutrophil-activating protein A (NapA), peptidoglycan (PG), vacuolating cytotoxin A (VacA) and the cag pathogenicity island (\textit{cagPAI}) including cytotoxin-associated gene A (CagA).\textsuperscript{18} Figure 1 provides an overview of \textit{H. pylori}'s colonization process and highlights bacterial factors that are important for persistence, survival and the initiation of immune responses. For a detailed description of relevant pathogenicity factors we would like to refer the reader to recent review articles on this topic.\textsuperscript{19,20}

Physical contact and the localization of \textit{H. pylori} within in the gastric mucosa are critical determinants for immunopathology. Approximately 20% of \textit{H. pylori} organisms in the stomach adhere to the surface of gastric epithelial cells.\textsuperscript{6} This physical contact causes cellular damage to the epithelium, induces inflammation and facilitates the delivery of toxins,\textsuperscript{21,22} which in turn promotes bacterial invasion and persistence. Upon CagA injection \textit{H. pylori} exploits the apical epithelial cell surface as a replicative niche.\textsuperscript{23} Furthermore, \textit{H. pylori} can establish colonies deep in the gastric glands (Fig. 1). The protein ChePep is necessary for this ability by regulating flagellar rotation through the chemotaxis system,\textsuperscript{24} and mutant \textit{H. pylori} strains lacking this chemotaxis ability are excellent tools for forming a comprehensive picture of how microscopic biogeography shapes the type and intensity of mucosal immune responses. Despite its initial classification as extracellular pathogen, recent studies revealed the facultative intracellular nature of \textit{H. pylori}. It invades and multiplies in gastric epithelial cells\textsuperscript{25,26} and adult epithelial progenitor cells\textsuperscript{27} thereby serving as a repository for \textit{H. pylori} and protecting it from antibiotic eradication. Although the mechanisms of invasion and persistence are not well understood, the importance of \textit{H. pylori} invasive NudA for host cell uptake was reported\textsuperscript{28} in vitro and dependence on c-Met and the type IV secretion system (T4SS) were determined.\textsuperscript{29}

Whether \textit{H. pylori} exerts a protective effect in the context of a dysregulated immune response or whether it contributes to immunopathology, cell damage and malignant transformation is dependent on host-pathogen interactions. The genetic background of both \textit{H. pylori} and the host contribute to disease etiology. On the microbial side the presence of an intact \textit{cagPAI}\textsuperscript{30} and the s1m1 variant of VacA among other factors have been associated with more severe pathology and an increased risk for gastroduodenal disease.\textsuperscript{31} The importance of the host’s immune response in delineating the outcome of chronic \textit{H. pylori} infection is reflected in the association of genetic polymorphisms with a higher risk for developing gastric cancer. These include IL-1\(\beta\),\textsuperscript{32} genes involved in Toll like receptor (TLR) and NOD-like receptor (NLR) signaling pathways\textsuperscript{33,34} and the immunoregulatory transcription factor peroxisome proliferator activated receptor \(\gamma\) (PPAR-\(\gamma\)).\textsuperscript{35} The relevance of these host factors will become apparent in the following sections discussing the current knowledge on innate and adaptive immune responses to \textit{H. pylori} and how its virulence factors influence these processes.

\textbf{Initiating the immune response to \textit{H. pylori}}

Sensing of pathogen associated molecular patterns (PAMPs) including PG, lipopolysaccharide (LPS),
flagellin and unmethylated CpG DNA by pathogen recognition receptors (PRRs) present on epithelial cells, antigen presenting cells and neutrophils is required for the initiation of immune responses to *H. pylori*. Recognition of PAMPs is mediated by membrane-bound TLRs, retinoic acid-inducible gene 1 (RIG-I)-like receptors, cytosolic NLRs and C-type lectins.36

The T4SS plays a crucial role in initiating immune responses to *H. pylori*. Upon contact with the host cell it forms a needle-like structure which protrudes from the bacterial surface and delivers virulence factors (e.g. CagA and PG) into the host cell.37,38 Intracellular PG is specifically recognized by NOD1 and causes the phosphorylation of MAPK, the activation of NF-κB as well as AP-1 and subsequent release of IL-8 by

---

**Figure 1.** Colonization of the gastric niche and initiation of immune responses by *H. pylori*. *H. pylori* possesses a number of virulence factors that aid in its ability to colonize and exploit the gastric niche for survival and replication. It elevates the gastric pH by secretion of urease and traverses the mucus layer through flagellar movement and urease-induced gel-sol transition. Once in contact with the epithelial cell layer it binds to the apical cell surface using various adhesins (SabA, BabA/B, AlpA/B, HopZ, OMP) causing cell damage and facilitating the delivery of toxins. *H. pylori* disrupts the cell barrier by breaking up tight- and adherent junctions (TJ, AJ) through HtrA and enters the lamina propria to replicate at the basolateral cell surface. *H. pylori* further exploits gastric glands and the apical cell surface as replicative niche for which the proteins Chepep and the virulence factor CagA respectively are essential. At the basolateral cell surface *H. pylori* forms the type 4 secretion system (T4SS) encoded by the cag pathogenicity island and causes integrin clustering at lipid rafts to inject CagA into epithelial cells. Peptidoglycan (PG) leaks through the T4SS and is recognized by the pathogen recognition receptor (PRR) NOD1. These two virulence factors induce the transcription of host-cell genes including IL-8, chemokines and type-I interferons (type-I IFN) through NFκB/AP1 and IRF7, respectively. *H. pylori* further causes host cell remodeling and damage through VacA. This toxin either heterodimerizes and forms pores in the cell membrane or enters by receptor binding to cause cell-vacuolization, pro-inflammatory cytokine signaling and cytochrome C (CytC)-induced apoptosis. Epithelial cells at the mucosal barrier are involved in initiating the immune response to *H. pylori* by antigen-induced TLR-2 and -4 signaling through NFκB. This is further amplified by the induction of TLR-4 transcription via NF-Y-mediated TLR-2 signaling. The subsequent secretion of chemokines attracts peripheral mononuclear cells (PMN) including neutrophils and dendritic cells to the site of infection.
epithelial cells.39,40 NOD1-mediated NF-κB activation is dependent on the delivery of PG into the host cell via the T4SS and requires the interaction with host α5β1 integrin localized to lipid rafts of AGS cells.41 Cholesterol-rich microdomains, also known as lipid rafts, are important sites for receptor complex formation upon H. pylori LPS recognition by TLRs. In AGS cells the induction of the TLR4/MD2 complex by H. pylori is dependent on the integrity of lipid rafts, where H. pylori, TLR4 and ceramide co-localize.42 Furthermore, H. pylori LPS can induce the recruitment of TLR2 to lipid rafts and trigger the formation of receptor clusters involving TLR1, CD11b/CD18 and CD36 in human vascular endothelial cells.43

Several studies have demonstrated that H. pylori LPS only signals via TLR244-47 while others demonstrated signaling via TLR4.32,48 Despite these controversial results it has been established that both TLR2 and 4 play a role in H. pylori LPS-mediated immune responses. Yokota et al.49 were able to provide an experimental link between TLR2 and TLR4 signaling in a gastric epithelial cell line. They show that H. pylori LPS binding to TLR2 activates the MEK1/2-ERK1/2 pathway which leads to NF-Y-mediated transcription of TLR4 and results in IL-8 secretion.49

Overall, recognition of H. pylori antigens by epithelial cells culminates in chemokine secretion (IL-8, CXCL1, CXCL2, CXCL3 and CCL20) and subsequently leads to the recruitment of neutrophils, eosinophils, monocytes, dendritic cells and macrophages.50,51 Macrophages located at sites of neutrophil infiltration in the lamina propria, gastric epithelium infiltrated by neutrophils as well as neutrophils themselves have been reported to express high levels of Gro-α and IL-8, two neutrophil-attractant chemokines.52 Furthermore, the upregulation of MIP-3α expression in gastric epithelial cells induces an influx of myeloid dendritic cells (DC) into the lamina propria as demonstrated in neonatally thymectomized BALB/c mice.53

In the following section we will discuss the current knowledge on sensing of H. pylori by innate immune cells and how this paves the way for the mixed pro- and anti-inflammatory adaptive immune responses typically observed in H. pylori infection.

**Innate immune responses to H. pylori**

In cultured human neutrophils H. pylori initiates an early innate immune response, which is partially mediated by TLR2 and TLR4, and characterized by rapid upregulation of IL-8, IL-1β and TNF-α followed by an increase in IL-10 production.54 Furthermore, H. pylori NapA, an agonist of TLR2, induces IL-12 and IL-23 secretion by neutrophils as well as monocytes and elicits an antigen-specific Th1 response in the gastric mucosa of H. pylori infected patients.55 Recognition of H. pylori PAMPs by antigen presenting cells, triggers the production of pro- and anti-inflammatory cytokines including IL-1, IL-6, IL-8, IL-10, IL-12 and type 1 IFN.56 Rad et al.57 identified 3 gene clusters that were upregulated in H. pylori-stimulated DC, i. MyD88 independent and MyD88-dependent mediated by ii. surface TLRs and iii. endosomal TLRs (Fig. 2). MyD88-independent expression of type-I IFNs and interferon-stimulated genes in DC is elicited by binding of H. pylori RNA to RIG-1 (Fig. 2).57 The main surface PRRs involved in H. pylori sensing by DC are TLR2 and to a lesser extent TLR4.57 Both surface TLRs play a dual role in H. pylori pathogenesis. Although TLR2 signaling participates in the induction of pro-inflammatory responses, transcriptome analysis of H. pylori-treated DC also revealed a TLR2-dependent anti-inflammatory signature in mice.57 Indeed, the lack of TLR2 in H. pylori infected mice induced a higher IFN-γ-mediated Th1 response and lower Treg/Th17 cell responses resulting in increased bacterial clearance at the expense of lesion development.58 In human DC this dual pro-and anti-inflammatory role seems to be conferred by TLR4 which has been shown to be the main contributor to H. pylori-induced IL-10 and IL-12p70 mediated Th1 induction. Neutralization of TLR-4 led to reduced IFN-γ, IL-17A and IL-10 secretion as well as FOXP3 expression in H. pylori-primed DC-T cell co-cultures.59 The endosomal TLR9 recognizing H. pylori DNA contributes significantly to the cytokine response (IL-6, IL-12) elicited by the bacterium. Interestingly, it also plays a role in the suppression of H. pylori-induced gastritis in the early phase by downregulating Th1 cytokines mediated by IFN-α (Type-I IFN).60

Another immune sensing mechanism playing an important role in immune responses toward H. pylori is the inflamasome. As a multi-protein complex it mediates the activation of CASP1 which promotes the secretion of the pro-inflammatory cytokines IL-1β and IL-18. Members of the NOD-like receptor family including NLRP1, NLRP3 and NLRC4 and the adapter ASC are critical components of the inflamasome.
which link microbial and endogenous danger signals to caspase 1 (CASP1) activation.\(^6\) In the context of *H. pylori* infection, the concomitant activation of TLR2 and NOD2 has been shown to induce pro-IL-1β expression and subsequent IL-1β secretion by *H. pylori*-infected DC. Dependency on CASP1 activation through priming of the NLRP3 inflammasome was demonstrated *in vitro* (Fig. 2).\(^6\) A recent study by Semper et al.\(^6\) further corroborates these findings and identifies potassium influx, phagocytosis and ROS production as mechanisms involved in *H. pylori*-mediated NLRP3 activation. Adhesion of *H. pylori* to the host cell and the *cag*PAI, but not CagA, were important for inflammasome activation in murine DC.

---

**Figure 2.** Innate immune sensing of *H. pylori*. The innate immune response to *H. pylori* is initiated by epithelial cells and tissue resident macrophages. Upon chemokine secretion dendritic cells are recruited to the gastric mucosa, where they encounter, recognize and process various known and unknown *H. pylori* antigens. Myd88-dependent TLR2 (LPS, NapA) and TLR4 (LPS) antigen binding results in both pro- and anti-inflammatory cytokine production which reflects the complexity of the immune response initiated by *H. pylori*. Following phagocytosis bacterial DNA is bound by TLR9 on endosomes and induces transcription of pro-inflammatory cytokines and type-I interferons (IFN) through NFKβ and IRF7/IRF8, respectively. Bacterial RNA is recognized by RIG-I and elicits Myd88-independent signaling to induce transcription of type-I IFN. Furthermore, inflammasome priming is mediated by binding of peptidoglycan (PG) to NOD2 and subsequent activation of NFκB-mediated transcription of pro-IL-1β. Subsequently, the inflammasome complex NLRP3/ASC/pro-Casp1 is activated by potassium efflux and phagocytosis-induced ROS production, which results in Casp1-mediated cleavage of pro-IL-1β to IL-1β.
and human monocytes/macrophages (Fig. 2). Moreover, *H. pylori* infected NLRP3-deficient mice showed increased bacterial colonization and decreased inflammation associated with decreased levels of IL-1β, IL-18, IL-17 and IFN-γ in the gastric mucosa. Similarly ASC-deficient mice showed higher colonization and less inflammation upon *H. pylori* infection.

Furthermore, the expression of NLRP12 and NLRX1, two negative regulators of NF-κB, were downregulated in THP-1-derived macrophages upon infection with the highly virulent *H. pylori* strain GC026 isolated from a gastric cancer patient. In concordance, NF-κB and several of its target genes including IFNB1, IL12B, IL6, TNF, CXCL1, CXCL2, CCL5, PTGS2 and BIRC3 were upregulated. In line with these findings, we recently validated that intracellular *H. pylori* modulates the dynamics of NLRX1 and NLRC3 expression, another regulatory NLR, and simultaneously induces NF-κB responsive genes in bone marrow derived macrophages. Interestingly, NLRX1 was necessary for maintaining high levels of intracellular *H. pylori* at the cellular level and in a murine model of infection. The contribution of NLRX1 in modulating host immunity to *H. pylori* may be associated with the combined effect of disruption of RIG-I signaling and inhibition of NF-κB activation by TRAF6 as observed in other infectious disease models, or a yet undiscovered pathway.

Suppression of regulatory NLRs is associated with worsened immunopathology in both immune mediated and infectious diseases but mechanisms of negative regulation have not been described.

The following section reviews the molecular mechanisms and complex cellular interactions that underlie the pro- and anti-inflammatory adaptive immune responses to *H. pylori* and how this contributes to chronic gastritis.

**Th1/Th17 responses to *H. pylori* infection**

Consistent with the induction of Th1 and Th17 responses, *H. pylori*-treated DC stimulate the secretion of IFN-γ and high levels of IL-17 by CD4+ T cells. Furthermore, murine splenic macrophages stimulated with *H. pylori* significantly upregulated gene expression of Th1- and Th17-inducing cytokines including IL-6, TGF-β, IL-23 p19, IL-12/IL-23 p40 and IL-12 p35 (Fig. 3). Even though *H. pylori*-pulsed DC secrete only low levels of IL-12 (p35/p40), robust IL-23 (p19/p40) expression is induced. Importantly, IL-23 was also detected in gastric myeloid DC of *H. pylori*-infected patients and expression of IL-23 p19 was increased in gastric epithelial cells of patients with *H. pylori*-associated gastritis, suggesting a potential role for epithelial cells in shaping mucosal immunity. *IL-23* belongs to the IL-12 family of cytokines and is known to promote the expansion and survival of Th17 cells. Indeed, blocking of endogenous IL-23 in cultures of lamina propria mononuclear cells from *H. pylori*-infected patients inhibited STAT3 phosphorylation and consequently diminished IL-17 secretion.

The virulence factors CagA and CagE have been implicated in the induction of IL-17 and IL-23 secretion further corroborating the significance of the cagPAI in *H. pylori* immunopathology. The cytokine BAFF, released by macrophages upon *H. pylori* infection, has recently been implicated in the induction of *H. pylori*-mediated Th17 responses in humans. BAFF has been shown to induce Th17 differentiation directly or indirectly through the creation of a pro-Th17 cytokine milieu by innate immune cells.

**Regulatory T cell responses to *H. pylori***

Despite the induction of mixed pro-inflammatory T cell responses, the immune system is unable to clear *H. pylori* resulting in life-long colonization. An underlying regulatory immune response which is induced by known and unknown bacterial factors and executed by regulatory T cells has been attributed to *H. pylori*’s ability to persist in its host. Although *H. pylori*-pulsed DC increase the production of IL-12 and induce secretion of Th1 cytokines (TNF-α, IFN-γ) as well as proliferation of murine splenocytes (Fig. 3), this response is much lower compared to DC pulsed with the Gram-negative bacillus *Acinetobacter iwofii*. A heat stable soluble factor released by *H. pylori* has been found to suppress IL-12 secretion by *A. iwofii*-stimulated DC. Another study recently demonstrated that *H. pylori* VacA suppressed IFN-β and IL-12 expression in murine bone marrow derived macrophages stimulated with *Lactobacillus acidophilus*. Furthermore, gastric and intestinal stroma-conditioned medium has been shown to down-regulate DC responsiveness to *H. pylori* in vitro. A yet unknown stromal factor inhibited monocyte-derived DC activation and impaired IL-12 release upon *H. pylori* infection consequently resulting in the reduced ability of
H. pylori-pulsed DC to induce an IFN-γ mediated Th1 response. Together, these studies suggest that both H. pylori- and host-derived factors might hinder the induction of a robust Th1 response through the suppression of IL-12 release by DC.

In line with the observation that H. pylori interferes with DC maturation in vitro, DC infiltrating the gastric mucosa of human H. pylori carriers exhibit a semimature DC-SIGN⁺HLA-DR⁺CD80⁺⁺⁺CD86⁺⁺⁺ phenotype. Specifically, H. pylori can trigger a reprogramming of DC by downregulating MHC-II, inducing IL-10 and inhibiting IL-12 secretion thereby inducing H. pylori specific Treg cells. CagA has been identified as the main virulence factor responsible for induction of semi-mature DC, IL-10-mediated STAT3 activation and subsequent Treg induction. Increased numbers of Treg cells are typically found in the stomachs of infected patients, suggesting that they play an important role in regulating inflammatory responses to H. pylori. In children, H. pylori infection favors the induction of mucosal Treg responses over Th17 and is thus associated with reduced gastric inflammatory lesions compared to adults. Overall, patients with fewer or less functional Treg cells are more likely to develop peptic ulcers and are afflicted by more intense gastritis. B cells also play a regulatory role by
promoting IL-10 production in co-cultured CD4+ cells and subsequent conversion into a T regulatory 1 (Tr1)-like phenotype. The importance of Treg cells for the control of *H. pylori*-induced gastritis has been highlighted in several studies. Adoptive transfer of C57BL/6 derived CD4+ splenocytes into *H. pylori*-infected RAG-KO mice lacking Treg induced more severe gastritis compared to *H. pylori*-infected C57BL/6 mice. Moreover, depletion of Treg cells resulted in decreased bacterial colonization at the expense of increased gastric inflammation.

One host cell factor on the intersection between pro- and anti-inflammatory responses toward *H. pylori* is the enzyme CASP1. Upon activation by the inflammasome complex it dynamically regulates immune responses through IL-1β and IL-18, respectively. IL-1 signaling is required for the induction of Th17 responses and IL-18 together with IL-12 is known to induce Th1 responses (reviewed in ). Albeit its pro-inflammatory role, the presence of IL-18 prevented excessive immunopathology and induced *H. pylori*-specific tolerance through the induction of Treg differentiation (Fig. 3), while its absence promoted unrestricted Th17 responses and IL-18 secretion from both CD8+ T cells and CD8+ T cells upon *H. pylori* antigen exposure. Interestingly, CD8+ T cells secreted even more IFN-γ than CD4+ T cells on a per cell basis. Studies in *H. pylori* infected children with grade I-III gastritis showed an increased number of CD8+ T cells in the gastric epithelium and lamina propria. Another study demonstrated an increase of CD8+HLA-DR+ chronically activated memory T cells in peripheral blood of *H. pylori*-colonized children with duodenal ulcers. We have recently demonstrated the expansion of circulating NK cells, CD8+ T cells and concomitant increases in cytotoxic markers including CD16, granzyme B and perforin in a pig model of *H. pylori* infection. Thus, a cytotoxic cell response might play a major role in *H. pylori*-mediated pathology at least in part due to the cytokine response induced by the bacterium.

Drivers of *H. pylori*-induced gastritis

To better understand, prevent and treat *H. pylori*-mediated disease one should identify the main factors involved in the development and sustainance of gastritis. A recent study by Gray et al. has shed further light on the complex interactions leading to *H. pylori*-induced gastritis. They determined that *H. pylori*-specific CD4+ T cells, innate immune cells expressing the common cytokine gamma chain and IFN-γ were essential for the development of gastritis in mice, whereas Th1 cells were not. This study suggests that IFN-γ secreted by other cell subsets (possibly functional innate immune cells) is the main driver of gastritis (Fig. 3). Thus far, NK cells and CD8+ cytotoxic T cells have been identified as additional source for IFN-γ in *H. pylori* infection. Yun et al. demonstrated that stimulation of human NK cells with *H. pylori* antigens induced IFN-γ production and increased the expression of granzyme B and perforin. Interestingly, *H. pylori*-induced IFN-γ secretion was dramatically increased in the presence of small doses of IL-12 p40. This synergistic effect was dependent on antigen exposure prior to addition of IL-12 and was associated with increased expression of IL-12 receptor β2 (Fig. 3). *H. pylori* specific membrane bound lipoprotein A (HpaA) has been implicated in the induction of IFN-γ secretion by NK cells, which was dependent on the recognition by TLR-2 and Myd88 as well as p38 MAPK signaling (Fig. 3). CD8+ T cells have also been implicated as a source for IFN-γ. A study assessing proliferation and cytokine secretion of circulating T cells from *H. pylori*-infected patients demonstrated induction of IFN-γ secretion from both CD4+ T cells and CD8+ T cells upon *H. pylori* antigen exposure. Interestingly, CD8+ T cells secreted even more IFN-γ than CD4+ T cells on a per cell basis. Studies in *H. pylori* infected children with grade I-III gastritis showed an increased number of CD8+ T cells in the gastric epithelium and lamina propria. Another study demonstrated an increase of CD8+HLA-DR+ chronically activated memory T cells in peripheral blood of *H. pylori*-colonized children with duodenal ulcers. We have recently demonstrated the expansion of circulating NK cells, CD8+ T cells and concomitant increases in cytotoxic markers including CD16, granzyme B and perforin in a pig model of *H. pylori* infection. Thus, a cytotoxic cell response might play a major role in *H. pylori*-mediated pathology at least in part due to the cytokine response induced by the bacterium.

While it has been established that IL-17A secretion and Th17 cells play a role in *H. pylori*-mediated gastritis their contribution is less dramatic than that of IFN-γ. Interestingly, recent studies have established an association between Th17 and Th1 responses. IL-17 deficiency in mice significantly reduced IFN-γ, T-bet and IL-12 p40 mRNA expression in gastric tissue of *H. pylori* infected animals suggesting that the Th17/IL-17 pathway plays a role in driving Th1 responses. Further to the association between Th17 and Th1 cells, Caruso et al. demonstrated that IL-23 does not only enhance IL-17 but also IFN-γ secretion by ex vivo stimulated normal human gastric lamina propria mononuclear cells. Blocking IL-23 in these cells significantly reduced IL-17 and IFN-γ secretion. Another molecule that has been implicated in *H. pylori*-induced gastritis is IL-21. IL-21 is a functional hallmark of T follicular helper (Tfh) cells, can also be produced by NKT cells, Th17 cells, and has been linked...
to Th1 and Th17 differentiation at the expense of Treg cell formation. Of note, we have recently identified the accumulation of cells with a Tfh phenotype (CD4+ T cells expressing CXCR5, ICOS, PD-1, BCL6, and IL-21) in the mesenteric lymph nodes and gastric lamina propria upon *H. pylori* infection in C57BL/6 mice.

Deficiency of IL-21 in *H. pylori*-infected mice resulted in increased bacterial burden and decreased inflammation characterized by highly reduced infiltration of neutrophils, B cells, CD4+ and CD8+ T cells into the stomach. The study also presented data showing that the mRNA expression of chemokines and cytokines including TNF-α, IL-1β, IL-17A and IFN-γ was inhibited in IL-21-deficient mice compared to their wild-type littermates upon *H. pylori* infection. This was associated with reduced expression of TBX1 and RORγt as well as reduced levels of activated STAT1 and STAT3. Thus, IL-21 contributes to the maintenance of both Th1 and Th17 responses.

Another recently described T cell subset that contributes to *H. pylori* induced gastritis are Th22 cells. Zhuang et al. show that Th22 cells are enriched in the gastric mucosa of *H. pylori*-infected patients and mice. They demonstrated that IL-23-secreting DC encountering *H. pylori* CagA+ strains highly induce secretion of IL-22 by CD4+ T cells. This leads to the recruitment of CXCR2+ monocyctic-myeloid derived suppressor cells (MDSC) into the gastric mucosa via IL-22R1 signaling and subsequent secretion of CXCL2 by gastric epithelial cells. Furthermore, MDSC secrete the two pro-inflammatory proteins S100A8/S100A9 upon IL-22 stimulation and suppress Th1 cell development. (Fig. 3).

**Mechanisms of immune evasion**

Consistent with its ability to chronically colonize the gastric microenvironment, *H. pylori* is equipped with efficient ways to evade recognition and clearance by the immune system. This is in part attributed to the expression of modified, less immunogenic PAMPs and to the secretion of certain pathogenicity factors, which alter the function of innate immune cells. Hence, *H. pylori* has the ability to evade, attenuate and modify innate and adaptive immune responses.

Modification of LPS, e.g., by adding positively charged substituents or removing phosphate groups from the backbone, renders *H. pylori* much less immunogenic than LPS from other gram-negative enteric bacteria such as *Escherichia coli*. The LPS component lipid A has been shown to bind to and activate the hTLR4-MD2 complex. Lipid A dephosphorylation by the enzymes LpxE and LpxF results in attenuated hTLR4-MD2 activation and confers resistance to the actions of cationic antimicrobial peptides thereby limiting the host's immune response and favoring *H. pylori*'s persistence.

Another mechanism of immune evasion is *H. pylori*'s ability to manipulate the function of innate immune cells. After successful phagocytosis by neutrophils, *H. pylori* disrupts the NADPH oxidative system thus enabling unopsonized *H. pylori* to escape phagocytic killing. Furthermore, *H. pylori* impairs neutrophil migration by decreasing the expression of CXCR1 and CXCR2. *H. pylori* induces the expression of arginase 2 (Arg2) in lamina propria macrophages thereby restricting iNOS upregulation, NO production and enhancing macrophage apoptosis. Accordingly, the expression of IFN-γ, IL17A and IL-12 p40 was increased and levels of IL-10 were decreased in the gastric antrum of Arg2/-/- mice.

Cyclooxygenase (COX)-2 is a key enzyme in arachidonic acid metabolism and induced by *H. pylori* via MEK/ERK signaling independent of the T4SS. Inhibition of COX-2 and its metabolic product prostaglandine E2 (PGE2) resulted in the increased production of IL-12 and IFN-γ and a decrease in IL-10 levels upon *H. pylori* infection suggesting that it contributes to the anti-inflammatory response against the bacterium.

Survival of *H. pylori* inside lamina propria macrophages also contributes to its ability to evade elimination by manipulating phagosome and autophagosome maturation. It impairs the antimicrobial activity of macrophages through the production of catalase and inhibits NO production by decreasing the availability of L-arginine through the bacterial arginase rocF as well as inhibiting L-arginine uptake by inducing spermine oxidase. Once engulfed, *H. pylori* is present in phagosomes and escape from phagocytic killing is dependent on cagPAL. VacA can arrest phagosome maturation by preventing its fusion with lysosomes, thus contributing to the pathogen’s persistence inside the cell. *H. pylori* uses host cholesterol to synthesize cholesterol-α-D-glucopyranoside (CG). This process is mediated through the enzyme cholesterol-
α-glucosyltransferase (CGT), encoded by capl. The presence of capl has been shown to confer resistance to phagocytic endocytosis, phagolysosome-fusion and -maturation. Furthermore, the synthesis of CG by CGT is responsible for retarded entry through the lipid-raft endocytic route and prolonged intracellular survival in a PI3K-dependent manner.122 H. pylori induces the formation of autophagosomes which are adapted for its replication and thus contribute to increased antimicrobial resistance.113 In primary human macrophages, virulent H. pylori strains can survive for an extended period due to the formation of megasomes, which are large structures arising from homotypic fusion of phagosomes.123

Additionally, H. pylori can directly limit adaptive immune responses by limiting nutrients essential for T-lymphocytes. The depletion of L-arginine by H. pylori arginase decreases the expression of CD3 zeta chains associated with the T cell receptor, thus inhibiting T cell proliferation.124 H. pylori γ-glutamyltranspeptidase depletes extracellular glutamine and consequently inhibits T lymphocyte proliferation, impairs activation and inhibits cytokine secretion involving IRF4.125 Endocytosis of VacA into activated human primary T cells inhibits cell proliferation and the clonal expansion of H. pylori antigen specific T-cells.127 It has also been shown that VacA can block T cell activation by preventing influx of extracellular calcium and subsequent nuclear translocation of NF-AT and by stimulating disordered actin polymerization through Rac activation.128

The beneficial role of H. pylori in extra-gastric disease

Since the identification of H. pylori as a causative agent of peptic ulcers and gastritis in 19834, the bacterium has been considered primarily a pathogen. However, infection with H. pylori is asymptomatic in 85% of individuals, only 15% develop symptomatic peptic ulcer, and less than 1% develop gastric cancer.129 A potential role of H. pylori as a gastric commensal or symbiotic bacterium is beginning to emerge in recent years. It has been demonstrated that H. pylori colonization even exerts beneficial effects in allergic diseases, such as asthma130 and eczema,131 as well as gastroesophageal reflux disease,132 obesity and diabetes.133 H. pylori’s ability to evade the immune system and to persist in the gastric mucosa through induction of Treg cells, regulatory CX3CR1+ mononuclear phagocytes, and anti-inflammatory molecules as discussed above lends further support to its potential role as a commensal organism.

It has been demonstrated that CD4+CD25+ T cells from H. pylori-infected neonatal WT mice are able to prevent the development of allergen-induced asthma in mice.80 Furthermore, H. pylori NapA has been shown to skew the immune response from a Th2 to a Th1 response in a mouse model of OVA-induced allergic asthma.134 In the context of immune-mediated diseases H. pylori infection protects against Salmonella typhi-induced colitis by suppressing Th17 responses in the lower intestinal tract and upregulating IL-10 expression in lymph nodes.135 Subsequent studies, demonstrated how H. pylori DNA decreases pro-inflammatory cytokine production by DC and attenuates sodium sulfate (DSS)-induced colitis in mice.136 Using a mouse model of DSS-induced and T-cell-transfer-induced colitis Engler et al.137 recently demonstrated a beneficial effect of H. pylori infection on clinical and histopathological features of colitis. They showed that H. pylori-mediated protection against DSS-induced colitis was dependent on the NLRP3 inflammasome and IL-18 signaling.137

Results from a study on the protective role of H. pylori in obesity, provide in vivo evidence that gastric colonization with a cagPAI negative H. pylori strain ameliorates glucose tolerance possibly by activating the transcription factor PPAR-γ. The presence of cagPAI negative H. pylori modulated appetite-controlling hormones (i.e., ghrelin and leptin), suppressed adipose tissue inflammation, and ameliorated glucose homeostasis. Interestingly, these effects were abrogated upon conditional knockout of PPAR-γ in immune- and epithelial cells.133 The inverse relationship between obesity and H. pylori colonization was recently studied in a North American cohort of inner city children revealing a 50% reduction in the odds of being obese when colonized with H. pylori.138

Recent epidemiological and clinical data indicate that the incidence of obesity139 and inflammatory bowel disease (IBD)140 is greater in areas with low prevalence of H. pylori infection. Whether this is due to a „spontaneous eradication“ of H. pylori caused by immunomodulatory drugs and antibiotics taken by IBD patients or due to an actual protective effect of H. pylori is still controversial.141 A study supporting
the causal association of *H. pylori* and IBD, reports that the rising incidence of IBD in *H. pylori*-endemic regions corresponds to the use of anti-*H. pylori* therapy for the treatment of peptic ulcer disease.\(^{142}\) Therefore, the evidence for *H. pylori*’s beneficial effects in allergic, immune-mediated and metabolic diseases seriously questions the validity of widespread *H. pylori* eradication strategies. Thus far, little is known about the relevance of virulence factors in *H. pylori*-mediated protection and this is likely to differ between diseases. In a study using data from 7663 participants of a large US National Health and Nutrition Examination Survey (NHANES III) Chen and Blaser\(^ {12}\) show that the infection with a more virulent CagA+ *H. pylori* strain was inversely associated with ever having had asthma in younger study participants. The beneficial effect of CagA+ strains in allergic disease and asthma can be at least partly explained by the increased IL-10 responses inducing semi-mature DC and higher Treg responses.\(^ {84,143}\) To date, no conclusive association between CagA status and Crohn’s disease has been made. Although a high frequency of Crohn’s disease patients was infected with CagA+ strains, this was similar to controls.\(^ {144}\) Thus, further pre-clinical and clinical studies as well as modeling studies are needed to strengthen and mechanistically characterize *H. pylori*’s role as beneficial member of the gut microbiota.

*H. pylori* infection provides an excellent avenue to probe mucosal immune responses and study mechanisms of immunoregulation and host tolerance that reduce the negative impact of infection on host fitness. Unlike resistance mechanisms, tolerance does not directly affect microbial burden. Rather, tolerance decreases the host susceptibility to tissue damage, or other fitness costs, caused by the pathogens or by the immune response against them. Given the co-evolution of *H. pylori* and its human host, studying mechanisms of *H. pylori*-host interaction may yield novel insights on how the human host can protect itself from infectious diseases by reducing the negative impact of infection on host fitness, independently of modulating the microbial burden. New integrative analyses can help synthesize and transform data, procedural knowledge and theory into information processing representations of immune responses to *H. pylori* with the potential to yield transformative systems-wide immunological knowledge.

**Computational modeling to advance our understanding of the complex interactions between *H. pylori* and the gastric immune system**

The interaction between *H. pylori* and the stomach mucosa is a complex and dynamic process. Computational modeling can be used to support pre-clinical and clinical research in *H. pylori* and to identify emerging behaviors of the immune response. We developed a tissue-model of the immune response to infection that represents the gastric lumen, epithelium, lamina propria and lymph nodes.\(^ {145}\) The model was calibrated with data from an *in vivo* time-course study of *H. pylori*-challenged mice and reproduced the effector and regulatory pathways in the gastric lamina propria, including the induction of a Th17 response, a dominant Th1 response and high levels of mucosal Treg.\(^ {145}\) Computational models can be used to study new therapeutic targets in the context of disease processes. To shed light on the potential role of the transcription factor PPAR-\(\gamma\) in modulating host responses to *H. pylori* we used a loss-of-function approach. *In silico* results predicted a predominance of Th17 and Th1 responses in cell-specific PPAR-\(\gamma\) knockout compared to WT mice.\(^ {145}\) Sensitivity analysis was used to rank immunological parameters by their relevance in the system’s dynamics and outcomes. Global sensitivity analysis has revealed that epithelial cells and macrophages have the highest influence in the mucosal immune response to *H. pylori*. The prediction of the impact of epithelial cells support the model itself, since most of *H. pylori* is found in contact with epithelium,\(^ {24,146,147}\) and the epithelial cell has been implicated in the initiation of innate responses (as discussed above).

With regards to macrophages, the analysis predicts the initial presence of macropage precursors, followed by the accumulation of a subset of M2 regulatory cells, which peaks between days 21 and 35. Interestingly, through the guidance of our computer modeling work, we have recently identified a CX3CR1+CD64+CD11b+F4/80+ subset of macrophages\(^ {148}\) (unpublished data) that starts accumulating in the stomach of mice at day 15, peaks around day 24 and it is maintained at a steady state for at least 16 weeks. These macrophages produce IL-10 and by depletion studies we have demonstrated that they facilitate colonization by *H. pylori*. 
In addition to the tissue-level computational model that can scale up to 10 billion cells and molecules at a time, we have engineered a model representing signaling events leading to CD4+ T cell differentiation and plasticity.104,149,150 Our cell-based model is generic in the sense that it represents CD4+ T cell differentiation out of any particular context,149,150 although it can be recalibrated with data obtained during infection. To investigate the role of IL-21 during H. pylori infection, we re-calibrated the model with CD4 data obtained from mice infected with H. pylori and used to construct an IL-21 knockout system.104 The main prediction of the model was the reciprocal interplay between IL-21 and IL-10 whereby, in the context of an H. pylori infection, IL-21 promotes differentiation of CD4+ T cells into Th1 and Th17 and opposes IL-10, and vice versa: lack of IL-21 turns the system in favor of IL-10. The predictions of the model were the validated in vivo using IL-21 KO mice. Others have also used mathematical modeling to evaluate the expression of pro and anti-inflammatory cytokines, and how their levels are affected by sonic hedgehog (SHH),151 a gene product that is upregulated in gastric parietal cells early post-H. pylori infection and has been proposed to be a macrophage chemoattractant.152

In summary, integrating computational and mathematical approaches to guide pre-clinical and clinical experimentation into the analysis of the host response to H. pylori can help accelerate the discovery of the mechanisms of action that explain the role of this microbe as pathogen or commensal microbe. Modeling and informatics tools that create information processing representations of immunological processes allow connecting immunology and microbiology to the world above the skin, testing interventions in virtual laboratories to guide human studies.

Disclosure of potential conflicts of interest
No potential conflicts of interest were disclosed.

Funding
This work was supported in part by NIAID Contract No. HHSN272201000056C to J.B.-R. and funds from the Nutritional Immunology and Molecular Medicine Laboratory.

References
1. Ndip RN, MacKay WG, Farthing MJG, Weaver LT. Culturing Helicobacter pylori from clinical specimens: review of microbiologic methods. J Pediatr Gastroenterol Nutr 2003; 36:616-22; PMID:12717085; http://dx.doi.org/10.1097/00005176-200305000-00005
2. McNulty SL, Mole BM, Dalidiene D, Segal I, Ally R, Mistry R, Secka O, Adegbola RA, Thomas JE, Lenarcic EM, et al. Novel 180- and 480-base-pair insertions in African and African-American strains of Helicobacter pylori. J Clin Microbiol 2004; 42:5658-63; PMID:15583296; http://dx.doi.org/10.1128/JCM.42.12.5658-5663.2004
3. Mane SP, Dominguez-Bello MG, Blaser MJ, Sobral BW, Hontecillas R, Skoneczka J, Mohapatra SK, Crasta OR, Evans C, Modise T, et al. Host-interactive genes in American Indian Helicobacter pylori diverge from their Old World homologs and mediate inflammatory responses. J Bacteriol 2010; 192:3078-92; PMID:20400544; http://dx.doi.org/10.1128/JB.00663-10
4. Marshall BJ, Warren JR. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. Lancet 1984; I:1311-5; PMID:6145023; http://dx.doi.org/10.1016/S0140-6736(84)91816-6
5. Danesh J. Helicobacter pylori infection and gastric cancer: systematic review of the epidemiological studies. Aliment Pharmacol Ther 1999; 13:851-6; PMID:10383517; http://dx.doi.org/10.1046/j.1365-2036.1999.00546.x
6. Permin H, Andersen LP. Inflammation, immunity, and vaccines for Helicobacter infection. Helicobacter 2005; 10 Suppl 1:21-5; PMID:16178967; http://dx.doi.org/10.1111/j.1523-5378.2005.00337.x
7. Blaser MJ. Disappearing microbiota: Helicobacter pylori protection against esophageal adenocarcinoma. Cancer Prev Res (Phila) 2008; I:308-11; PMID:19138974; http://dx.doi.org/10.1158/1940-6207.CAPR-08-0170
8. Vieth M, Masoud B, Meining A, Stolte M. Helicobacter pylori infection: protection against Barrett’s mucosa and neoplasia? Digestion 2000; 62:225-31; PMID:11070405; http://dx.doi.org/10.1159/000007820
9. Vaezi MF, Falk GW, Peek RM, Vicari JJ, Goldblum JR, Perez-Perez GI, Rice TW, Blaser MJ, Richter JE. CagA-positive strains of Helicobacter pylori may protect against Barrett’s esophagus. Am J Gastroenterol 2000; 95:2206-11; PMID:11007219; http://dx.doi.org/10.1111/j.1572-0241.2000.02305.x
10. Chow WH, Blaser MJ, Blot WJ, Gammon MD, Vaughan TL, Risch HA, Perez-Perez GI, Schoenberg JB, Stanford JL, Rotterdam H, et al. An inverse relation between cagA+ strains of Helicobacter pylori infection and risk of esophageal and gastric cardia adenocarcinoma. Cancer Res 1998; 58:588-90; PMID:9485003
11. Lang L. Childhood acquisition of Helicobacter pylori linked to reduced asthma and allergy risk. Gastroenterology 2007; 133:6; PMID:17631119; http://dx.doi.org/10.1053/j.gastro.2007.05.011
12. Chen Y, Blaser MJ. Inverse associations of Helicobacter pylori with asthma and allergy. Arch Intern Med 2007; 167:821-7; PMID:17452546; http://dx.doi.org/10.1001/archinte.167.8.821
45. Mandell L, Moran AP, Cocchiarella A, Houghton J, Taylor N, Fox JG, Wang TC, Kurt-Jones EA. Intact gram-negative Helicobacter pylori, Helicobacter felis, and Helicobacter hepticus bacteria activate innate immunity via toll-like receptor 2 but not toll-like receptor 4. Infect Immun 2004; 72:6446-54; PMID:15501775; http://dx.doi.org/10.1128/IAI.72.11.6446-6454.2004

46. Yokota S, Ohnishi T, Muroi M, Tanamoto K, Fujii N, Amano K. Highly-purified Helicobacter pylori LPS preparations induce weak inflammatory reactions and utilize Toll-like receptor 2 complex but not Toll-like receptor 4 complex. FEMS Immunol Med Microbiol 2007; 51:1-40; 8; PMID:17645528; http://dx.doi.org/10.1111/j.1574-695X.2007.00288.x

47. Smith SM, Moran AP, Duggan SP, Ahmed SE, Mohamed AS, Windle HJ, O’Neill LA, Kelleher DP. Tribbles 3: a novel regulator of TLR2-mediated signaling in response to Helicobacter pylori lipopolysaccharide. J Immunol 2011; 186:2462-71; PMID:21220698; http://dx.doi.org/10.4049/jimmunol.1000864

48. Cullen TW, Giles DK, Wolf LN, Ecobichon C, Boneca IG, Trent MS. Helicobacter pylori vs. the host: remodeling of the bacterial outer membrane is required for survival in the gastric mucosa. PLoS Pathog 2011; 7: e1002454; PMID:22216004; http://dx.doi.org/10.1371/journal.ppat.1002454

49. Yokota SI, Okabayashi T, Rehli M, Fujii N, Amano KI. Helicobacter pylori lipopolysaccharides upregulate toll-like receptor 4 expression and proliferation of gastric epithelial cells via the MEK1/2-ERK1/2 mitogen-activated protein kinase pathway. Infect Immun 2010; 78:468-76; PMID:19858308; http://dx.doi.org/10.1128/IAI.00903-09

50. Backert S, Naumann M. What a disorder: proinflammatory signaling pathways induced by Helicobacter pylori. Trends Microbiol 2010; 18:479-86; PMID:20863705; http://dx.doi.org/10.1016/j.tim.2010.08.003

51. Nagy TA, Allen SS, Wroblewski LE, Flaherty DK, Slaughter JC, Perez-Perez G, Isreal DA, Peek RM. Helicobacter pylori induction of eosinophil migration is mediated by the cag pathogenicity island via microbial-epithelial interactions. Am J Pathol 2011; 178:1448-52; PMID:21406172

52. Eck M, Schmausser B, Scheller K, Toksoy A, Kraus M, Menzel T, Müller-Hermelink HK, Gillitzer R. CXC chemokines Gro(α)/IL-8 and IP-10/MIG in Helicobacter pylori gastritis. Clin Exp Immunol 2000; 122:192-9; PMID:11091274; http://dx.doi.org/10.1046/j.1365-2249.2000.01374.x

53. Nishi T, Okazaki K, Kawasaki F, Fukui T, Tamaki H, Matsuura M, Asada M, Watanabe T, Uchida K, Watanabe N, et al. Involvement of myeloid dendritic cells in the development of gastric secondary lymphoid follicles in Helicobacter pylori-infected neonatally thymectomy,ized BALB/c mice. Infect Immun 2003; 71:2153-62; PMID:12654837; http://dx.doi.org/10.1128/IAI.71.4.2153-2162.2003

54. Alvarez-Arellano L, Camorlinga-Ponce M, Maldonado-Bernal C, Torres J. Activation of human neutrophils with Helicobacter pylori and the role of Toll-like receptors 2 and 4 in the response. FEMS Immunol Med Microbiol
55. Amedei A, Cappon G, Codolo G, Cabarella A, Polenghi A, Benagiano M, Tasca E, Azzurri A, D’Elios MM, Del Prete G, et al. The neutrophil-activating protein of Helicobacter pylori promotes TH1 immune responses. J Clin Invest 2006; 116:1092-101; PMID:16543949; http://dx.doi.org/10.1172/JCI27177

56. Rad L, Ballhorn W, Voland P, Eisenacher K, Mages J, Rad L, Ferstl R, Lang R, Wagner H, Schmid RM, et al. Extracellular and intracellular pattern recognition receptor cooperates in the recognition of Helicobacter pylori. Gastroenterology 2009; 136:2247-57; PMID:19272387; http://dx.doi.org/10.1053/j.gastro.2009.02.066

57. Sun X, Zhang M, El-Zataari M, Owyang SY, Eaton KA, Benoît BN, Kobayashi M, Kawakubo M, Takeoka M, Sano KM, Zhang M, El-Zataari M, Owyang SY, Eaton KA, Benoît BN, Kobayashi M, Kawakubo M, Takeoka M, Sano KM, Zou J, Itano N, Tsutsui H, Noda T, Fukuda M, et al. Role of ASC in the mouse model of Helicobacter pylori infection. J Histochem Cytochem 2009; 57:327-38; PMID:19064716; http://dx.doi.org/10.1369/jhc.2008.952366

58. Käbisch R, Mejías-Luque R, Gerhard M, Prinz C. Involvement of Toll-Like Receptors on Helicobacter pylori-Induced Inflammation. PLoS One 2014; 9:e104804; http://dx.doi.org/10.1371/journal.pone.0104804

59. Otani K, Tanigawa T, Watanabe T, Nadatani Y, Sogawa M, Yamagami H, Shiba M, Watanabe K, Tominaga K, Fujisawa Y, et al. Toll-like receptor 9 signaling has anti-inflammatory effects on the early phase of Helicobacter pylori-induced gastritis. Biochem Biophys Res Commun 2012; 426:342-9; PMID:22940550; http://dx.doi.org/10.1016/j.bbrc.2012.08.080

60. Franchi L, Eigenbrod T, Muñoz-Planillo R, Nuñez G. The inflammasome: a caspase-1-activation platform that regulates immune responses and disease pathogenesis. Nat Immunol 2009; 10:241-7; PMID:19221555; http://dx.doi.org/10.1038/ni.1703

61. Kim DJ, Park JH, Franchi L, Backert S, Nuñez G. The Cag pathogenicity island and interaction between TLR2/NOD2 and NLRP3 regulate IL-1β production in Helicobacter pylori infected dendritic cells. Eur J Immunol 2013; 43:2650-8; PMID:23818043; http://dx.doi.org/10.1002/eji.201243281

62. Semper RP, Mejías-Luque R, Groß C, Anderl F, Müller A, Vieth M, Busch DH, Prazeres da Costa C, Ruland J, Groß O, et al. Helicobacter pylori-Induced IL-1β Secretion in Innate Immune Cells Is Regulated by the NLRP3 Inflammasome and Requires the Cag Pathogenicity Island. J Immunol 2014; 193:3566-76; PMID:25172489; http://dx.doi.org/10.4049/jimmunol.1400362

63. Benoît BN, Kobayashi M, Kawakubo M, Takeoka M, Sano K, Zou J, Itano N, Tsutsui H, Noda T, Fukuda M, et al. Role of ASC in the mouse model of Helicobacter pylori infection. J Histochem Cytochem 2009; 57:327-38; PMID:19064716; http://dx.doi.org/10.1369/jhc.2008.952366

65. Castaño-Rodríguez N, Kaakoush NO, Goh K-L, Fock KM, Mitchell HM. The NOD-like receptor signalling pathway in Helicobacter pylori infection and related gastric cancer: a case-control study and gene expression analyses. PLoS One 2014; 9:e998899; http://dx.doi.org/10.1371/journal.pone.0098899

66. Allen IC, Moore CB, Schneider M, Lei Y, Davis BK, Scull MA, Gris D, Roney KE, Zimmermann AG, Bowzard JB, et al. NLRX1 protein attenuates inflammatory responses to infection by interfering with the RIG-I-MAVS and TRAF6-NF-κB signaling pathways. Immunity 2011; 34:854-65; PMID:21703540; http://dx.doi.org/10.1016/j.immuni.2011.03.026

67. Xia X, Cui J, Wang HY, Zhu L, Matsueda S, Wang Q, Yang X, Hong J, Songyang Z, Chen ZJ, et al. NLRX1 negatively regulates TLR-induced NF-κB signaling by targeting TRAF6 and IKK. Immunity 2011; 34:843-53; PMID:21703559; http://dx.doi.org/10.1016/j.immuni.2011.02.022

68. Kang MJ, Yoon CM, Kim BH, Lee CM, Zhou Y, Sailer M, Homer R, Dhamija A, Boffa D, West AP, et al. Suppression of NLRX1 in chronic obstructive pulmonary disease. J Clin Invest 2015; 125:2458-62; PMID:25938787; http://dx.doi.org/10.1172/JCI71747

69. Lord CA, Savitsky D, Sitcheran R, Calame K, Wright JR, Ting JPY, Williams KL. Blimp-1/PRDM1 mediates transcriptional suppression of the NLR gene NLRP12/Mon-arch-1. J Immunol 2009; 182:2948-58; PMID:19234190; http://dx.doi.org/10.4049/jimmunol.0801692

70. Schneider M, Zimmermann AG, Roberts RA, Zhang L, Swanson K V, Chen Y, Blumenschein WM, Mattson J, Basham B, Sedgwick JD, McClanahan T, Kastelein RA, et al. IL-23 drives a pathogenic T cell population that...
induces autoimmune inflammation. J Exp Med 2005; 201:233-40; PMID:15657292; http://dx.doi.org/10.1084/jem.20041257

75. Caruso R, Fina D, Paoluzzi OA, Del Vecchio Blanco G, Stolfi C, Rizzo A, Caprioli F, Sarra M, Andrei F, Fantini MC, et al. IL-23-mediated regulation of IL-17 production in Helicobacter pylori-infected gastric mucosa. Eur J Immunol 2008; 38:470-8; PMID:18200634; http://dx.doi.org/10.1002/eji.200737635

76. Munari F, Fassan M, Capitani N, Codolo G, Vila-Cabalfer M, Pizzi M, Rugge M, Della Bella C, Troilo A, D’Elia S, et al. Cytokine BAFF released by Helicobacter pylori-infected macrophages triggers the Th17 response in human chronic gastritis. J Immunol 2014; 193:5584-94; PMID:25339679; http://dx.doi.org/10.1002/jimmunol.1302865

77. Kao JY, Rathinavelu S, Eaton K a, Bai L, Zavros Y, Takami K, Pizzi A, Caprilli A, Merchant JL. Helicobacter pylori-secreted factors inhibit dendritic cell IL-12 secretion: a mechanism of ineffective host defense. Am J Physiol Gastrointest Liver Physiol 2006; 291:G73-81; PMID:16469828; http://dx.doi.org/10.1152/ajpgi.00139.2005

78. Weiss G, Forster S, Irving A, Tate M, Ferrero RL, Hertzog W-D, Muller A, Macher A, Viviani P, Guiraldes E, et al. Helicobacter pylori gastritis in children is associated with a regulatory T-cell response. Gastroenterology 2008; 134:491-9; PMID:18242215; http://dx.doi.org/10.1053/j.gastro.2007.11.006

79. Bimczok D, Grams JM, Stahl RD, Waite KB, Smythies LE, Smith PD. Stromal regulation of human gastric dendritic cells restricts the Th1 response to Helicobacter pylori. Gastroenterology 2011; 141:929-38; PMID:21699795; http://dx.doi.org/10.1053/j.gastro.2011.06.006

80. Oertli M, Sundquist M, Hitzler I, Engler DB, Arnold IC, Reuter S, Maxeiner J, Hansson M, Taube C, Quiding-Le Flanker M, et al. DC-derived IL-18 drives Treg differentiation, murine Helicobacter pylori-specific immune tolerance, and asthma protection. J Clin Invest 2012; 122:1082-96; PMID:22307326; http://dx.doi.org/10.1172/JCI61029

81. Mitchell P, Germain C, Fiori PL, Khamri W, Foster GR, Ghosh S, Lechler RI, Bamford KB, Lombardi G. Chronic exposure to Helicobacter pylori impairs dendritic cell function and inhibits Th1 development. Infect Immun 2007; 75:810-9; PMID:17101659; http://dx.doi.org/10.1128/IAI.00228-06

82. Wang YH, Gorvel JP, Chu YT, Wu JJ, Lei HY. Helicobacter pylori impairs murine dendritic cell responses to infection. PLoS One 2010; 5:e10844; PMID:20523725; http://dx.doi.org/10.1371/journal.pone.0010844

83. Zhang M, Liu M, Luther J, Kao JY. Helicobacter pylori directs tolerogenic programming of dendritic cells. Gut Microbes 2010; 1:325-9; PMID:21327041; http://dx.doi.org/10.4161/gmic.1.5.13052

84. Kaebsch R, Mejias-Luque R, Prinz C, Gerhard M. Helicobacter pylori cytotoxin-associated gene A impairs human dendritic cell maturation and function through IL-10-mediated activation of STAT3. J Immunol 2014; 192:316-23; PMID:24293633; http://dx.doi.org/10.4049/jimmunol.1302476

85. Lundgren A, Trollmo C, Edebo A, Svennerholm AM, Lundin BS. Helicobacter pylori-secreted CD4+ T cells home to and accumulate in the human Helicobacter pylori-infected gastric mucosa. Infect Immun 2005; 73:5612-9; PMID:16113278; http://dx.doi.org/10.1128/IAI.73.9.5612-5619.2005

86. Serrano C, Diaz MI, Valdivia A, Godoy A, Peña A, Rollan A, Kirberg A, Hebel E, Fierro J, Klapp G, et al. Relationship between Helicobacter pylori virulence factors and regulatory cytokines as predictors of clinical outcome. Microbes Infect 2007; 9:428-34; PMID:17336120; http://dx.doi.org/10.1016/j.micinf.2006.12.012

87. Harris PR, Wright SW, Serrano C, Riera F, Duarte I, Torres J, Peña A, Rollán A, Viviani P, Guiraldes E, et al. Helicobacter pylori gastritis in children is associated with a regulatory T-cell response. Gastroenterology 2008; 134:491-9; PMID:18242215; http://dx.doi.org/10.1053/j.gastro.2007.11.006

88. Atherton JC, Blaser MJ. Coadaptation of Helicobacter pylori and humans: ancient history, modern implications. J Clin Invest 2009; 119:2475-87; PMID:19729845; http://dx.doi.org/10.1172/JCI38605

89. Muller A, Oertli M, Arnold IC. Helicobacter pylori exploits and manipulates innate and adaptive immune cell signaling pathways to establish persistent infection. Cell Commun Signal 2011; 9:25; PMID:22044597; http://dx.doi.org/10.1186/1478-811X-9-25

90. Gray BM, Fontaine C A, Poe S A, Eaton K A. Complex T cell interactions contribute to Helicobacter pylori gastritis in mice. Infect Immun 2013; 81:740-52; PMID:23264048; http://dx.doi.org/10.1128/IAI.01269-12

91. Luther J, Dave M, Higgins PDR, Kao JY. Association between Helicobacter pylori infection and inflammatory bowel disease: a meta-analysis and systematic review of the literature. Inflamm Bowel Dis 2010; 16:1077-84; PMID:19760778; http://dx.doi.org/10.1002/ibd.21116

92. Hitzler I, Sayi A, Kohler E, Engler DB, Koch KN, Hardt W-D, Muller A. Caspase-1 has both proinflammatory and regulatory properties in Helicobacter infections, which are differentially mediated by its substrates IL-1β and IL-18. J Immunol 2012; 188:3594-602; PMID:23604666; http://dx.doi.org/10.1128/mbio.00609-12

93. Atherton JC, Blaser MJ. Coadaptation of Helicobacter pylori and humans: ancient history, modern implications. J Clin Invest 2009; 119:2475-87; PMID:19729845; http://dx.doi.org/10.1172/JCI38605

94. Muller A, Oertli M, Arnold IC. Helicobacter pylori exploits and manipulates innate and adaptive immune cell signaling pathways to establish persistent infection. Cell Commun Signal 2011; 9:25; PMID:22044597; http://dx.doi.org/10.1186/1478-811X-9-25

95. Gray BM, Fontaine C A, Poe S A, Eaton K A. Complex T cell interactions contribute to Helicobacter pylori gastritis in mice. Infect Immun 2013; 81:740-52; PMID:23264048; http://dx.doi.org/10.1128/IAI.01269-12

96. Luther J, Dave M, Higgins PDR, Kao JY. Association between Helicobacter pylori infection and inflammatory bowel disease: a meta-analysis and systematic review of the literature. Inflamm Bowel Dis 2010; 16:1077-84; PMID:19760778; http://dx.doi.org/10.1002/ibd.21116

97. Hitzler I, Sayi A, Kohler E, Engler DB, Koch KN, Hardt W-D, Muller A. Caspase-1 has both proinflammatory and regulatory properties in Helicobacter infections, which are differentially mediated by its substrates IL-1β and IL-18. J Immunol 2012; 188:3594-602; PMID:22403439; http://dx.doi.org/10.4049/jimmunol.1302476

98. Yun CH, Lundgren A, Azem J, Sjöling A, Holmgren J, Svennerholm AM, Lundin BS. Natural killer cells and Helicobacter pylori infection: bacterial antigens and interleukin-12 act synergistically to induce gamma interferon production. Infect Immun 2005; 73:1482-90; PMID:15731046; http://dx.doi.org/10.1128/IAI.73.3.1482-1490.2005
95. Lindgren A, Pavlovic V, Flach CF, Sjöling A, Lundin S. Interferon-gamma secretion is induced in IL-12 stimulated human NK cells by recognition of Helicobacter pylori or TLR2 ligands. Innate Immun 2011; 17:191-203; PMID:21930107; http://dx.doi.org/10.1177/1753429909357970

96. Quiding-Järbrink M, Lundin BS, Lönnroth H, Svennerholm AM, CD4+ and CD8+ T cell responses in Helicobacter pylori-infected individuals. Clin Exp Immunol 2001; 123:81-7; http://dx.doi.org/10.1046/j.1365-2249.2001.01427.x

97. Krauss-Etschmann S, Gruber R, Plikat K, Antoni I, Demmelhain H, Reinhardt D, Koletzko S. Increase of antigen-presenting cells in the gastric mucosa of Helicobacter pylori-infected children. Helicobacter 2005; 10:214-22; PMID:15904479; http://dx.doi.org/10.1111/j.1153-5378.2005.00313.x

98. Lopes AI, Victorino RRM, Palha AM, Ruivo J, Fernandes A. Mucosal lymphocyte subsets and HLA-DR antigen expression in paediatric Helicobacter pylori-associated gastritis. Clin Exp Immunol 2006; 145:13-20; PMID:16792668; http://dx.doi.org/10.1111/j.1365-2249.2006.03100.x

99. Figueiredo Soares T, Aguiar Rocha G, Camargos Rocha AM, Corrêa-Oliveira R, Martins-Filho OA, Teles Carvalho AS, Souto Bittencourt PF, Afonso Oliveira C, Ferreira Nogueira AMM, Alves Cabrал MMD, et al. Differences in peripheral blood lymphocyte phenotypes between Helicobacter pylori-positive children and adults with duodenal ulcer. Clin Microbiol Infect 2007; 13:1083-8; PMID:17727678; http://dx.doi.org/10.1111/j.1469-0691.2007.01814.x

100. Kronsteiner B, Bassaganya-Riera J, Philipson C, Viladomiu M, Carbo A, Pedragosa M, Vento S, Hontecillas R. Helicobacter pylori infection in a pig model is dominated by Th1 and cytotoxic CD8+ T cell responses. Infect Immun 2013; 81:3803-13; PMID:23897614; http://dx.doi.org/10.1128/IAI.00660-13

101. Stolfi C, Rizzo A, Franzé E, Rotondi A, Fantini MC, Sarra M, Caruso R, Monteleone I, Sileri P, Franceschilli L, et al. Involvement of interleukin-21 in the regulation of colitis-associated colon cancer. J Exp Med 2011; 208:2279-90; PMID:21987656; http://dx.doi.org/10.1084/jem.20111106

102. Pallone F, Fina D, Caruso R, Monteleone G. Role of IL-21 in inflammatory bowel disease. Expert Rev Clin Immunol 2010; 6:537-41; PMID:20594126; http://dx.doi.org/10.1586/erci.10.44

103. Leber A, Abedi V, Hontecillas R, Viladomiu M, Hoops S, Ciupe S, Caugmann J, Andrew T, Bassaganya-Riera J. Bistability analysis of CD4+ T follicular helper and regulatory cells during Helicobacter pylori infection. J Theor Biol; under review

104. Carbo A, Olivares-Villagómez D, Hontecillas R, Bassaganya-Riera J, Chaturvedi R, Piazuelo MB, Delgado A, Washington MK, Wilson KT, Algood HMS. Systems modeling of the role of interleukin-21 in the maintenance of effector CD4+ T cell responses during chronic Helicobacter pylori infection. MBio 2014; 5:e01243-14; PMID:25053783; http://dx.doi.org/10.1128/mBio.01243-14

105. Zhuang Y, Cheng P, Liu XF, Peng LS, Li BS, Wang TT, Chen N, Li WH, Shi Y, Chen W, et al. A pro-inflammatory role for Th22 cells in Helicobacter pylori-associated gastritis. Gut 2015; 64:1368-78; PMID:25134787; http://dx.doi.org/10.1136/gutjnl-2014-307020

106. Muotiala A, Helander IM, Pyhälä I, Kosunen TU, Moran AP. Low biological activity of Helicobacter pylori lipopolysaccharide. Infect Immun 1992; 60:1714-6; PMID:1548097

107. Allen LAH, Beecher BR, Lynch JT, Rohner OV, Wittine LM. Helicobacter pylori disrupts NADPH oxidase targeting in human neutrophils to induce extracellular superoxide release. J Immunol 2005; 174:3658-67; PMID:15749904; http://dx.doi.org/10.4049/jimmunol.174.6.3658

108. Schmausser B, Josenhans C, Endrich S, Suerbaum S, Sitaru C, Andrusl M, Brändlein S, Rieckmann P, Müller-Hermelink HK, Eck M. Downregulation of CXCR1 and CXCR2 expression on human neutrophils by Helicobacter pylori: a new pathomechanism in H. pylori infection? Infect Immun 2004; 72:6773-9; PMID:15557597; http://dx.doi.org/10.1128/IAI.72.12.6773-6779.2004

109. Lewis ND, Asim M, Barry DP, de Sablet T, Singh K, Piazuelo MB, Gobert AP, Chaturvedi R, Wilson KT. Immune evasion by Helicobacter pylori is mediated by induction of macrophage arginase II. J Immunol 2011; 186:3632-41; PMID:21296975; http://dx.doi.org/10.4049/jimmunol.1003431

110. Jüttner S, Cramer T, Wessler S, Walduck A, Gao F, Schmitz F, Wunder C, Weber M, Fischer SM, Schmidt WE, et al. Helicobacter pylori stimulates host cyclooxygenase-2 gene transcription: critical importance of MEK/ERK-dependent activation of USF1/-2 and CREB transcription factors. Cell Microbiol 2003; 5:821-34; PMID:14531897; http://dx.doi.org/10.1046/j.1462-5822.2003.00324.x

111. Meyer F, Ramanujam KS, Gobert AP, James SP, Wilson KT. Cutting edge: cyclooxygenase-2 activation suppresses Th1 polarization in response to Helicobacter pylori. J Immunol 2003; 171:3913-7; PMID:14530307; http://dx.doi.org/10.4049/jimmunol.171.8.3913

112. Ozbek A, Ozbek E, Dursun H, Kalkan Y, Demirci T. Can Helicobacter pylori invade human gastric mucosa?: an in vivo study using electron microscopy, immunohistochemical methods, and real-time polymerase chain reaction. J Clin Gastroenterol 2010; 44:416-22; PMID:19904218

113. Wang Y, Wu J, Lei H. When Helicobacter pylori invades human gastric epithelia: a role for TLR2 and Dectin-1. J Pathol 2008; 216:33-42; PMID:18290314; http://dx.doi.org/10.1002/path.2258

114. Greenfield LK, Jones NL. Modulation of autophagy by Helicobacter pylori and its role in gastric carcinogenesis. Trends Microbiol 2013; 21:602-12; PMID:24156875; http://dx.doi.org/10.1016/j.tim.2013.09.004

115. Basu M, Czinn SJ, Blanchard TG. Absence of catalase reduces long-term survival of Helicobacter pylori in...
macrophage phagosomes. Helicobacter 2004; 9:211-6; PMID:15165256; http://dx.doi.org/10.1111/j.1083-4389.2004.00226.x

116. Gobert AP, McGee DJ, Akhtar M, Mendz GL, Newton JC, Cheng Y, Mobley HL, Wilson KT. Helicobacter pylori arginase inhibits nitric oxide production by eukaryotic cells: a strategy for bacterial survival. Proc Natl Acad Sci U S A 2001; 98:13844-9; PMID:11717441; http://dx.doi.org/10.1073/pnas.241443798

117. Chaturvedi R, Asim M, Lewis ND, Algood HMS, Cover TL, Kim PY, Wilson KT. L-arginine availability regulates inducible nitric oxide synthase-dependent host defense against Helicobacter pylori. Infect Immun 2007; 75:4305-15; PMID:17562760; http://dx.doi.org/10.1128/IAI.00578-07

118. Chaturvedi R, Asim M, Barry DP, Frye JW, Casero RA, Wilson KT. Spermine oxidase is a regulator of macrophage host response to Helicobacter pylori: enhancement of antimicrobial nitric oxide generation by depletion of spermine. Amino Acids 2014; 46:531-42; PMID:23820617; http://dx.doi.org/10.1007/s00726-013-1531-z

119. Rittig MG, Atherton JC. Helicobacter pylori-induced homotypic phagosome fusion in human monocytes is independent of the bacterial vacA and cag status. Cell Microbiol 2003; 5:887-99; PMID:14641174; http://dx.doi.org/10.1046/j.1462-5822.2003.00328.x

120. Ramarao N, Meyer TF. Helicobacter pylori resists phagocytosis by macrophages: quantitative assessment by confocal microscopy and fluorescence-activated cell sorting. Infect Immun 2001; 69:2604-11; PMID:11254625; http://dx.doi.org/10.1128/IAI.69.4.2604-2611.2001

121. Zheng PY, Jones NL. Helicobacter pylori strains expressing the vacuolating cytotoxin interrupt phagosome maturation in macrophages by recruiting and retaining TACO (coronin 1) protein. Cell Microbiol 2003; 5:25-40; PMID:12542468; http://dx.doi.org/10.1046/j.1462-5822.2003.00250.x

122. Du SY, Wang HJ, Cheng HH, Chen SD, Wang LHC, Wang WC. Cholesterol glucosylation by Helicobacter pylori delays internalization and arrests phagosome maturation in macrophages. J Microbiol Immunol Infect 2004; 37:1:51-61; PMID:23910799

123. Dewald X, Jiménez-Soto L, Haas R. PKC-dependent endocytosis of the Helicobacter pylori vacuolating cytotoxin in primary T lymphocytes. Cell Microbiol 2011; 13:482-96; PMID:21083636; http://dx.doi.org/10.1111/j.1462-5822.2010.01551.x

124. Sundrud MS, Torres VJ, Unutmaz D, Cover TL. Inhibition of primary human T cell proliferation by Helicobacter pylori vacuolating toxin (VacA) is independent of VacA effects on IL-2 secretion. Proc Natl Acad Sci U S A 2004; 101:7727-32; PMID:15128946; http://dx.doi.org/10.1073/pnas.0401528101

125. Wustner S, Mejias-Luque R, Koch MF, Rath E, Vieht M, Sieber SA, Haller D, Gerhard M. H. pylori γ-glutamyl-transpeptidase impairs T-lymphocyte function by compromising metabolic adaption through inhibition of cMyc and IRF4 expression. Cell Microbiol 2014; 17(1):51-61; PMID:23910799
attenuates dextran sodium sulphate-induced colitis. Gut 2011; 60:1479-86; PMID:21471567; http://dx.doi.org/10.1136/gut.2010.220087

137. Engler DB, Leonardt I, Hartung ML, Kyburz A, Spath S, Becher B, Rogler G, Müller A. Helicobacter pylori-specific protection against inflammatory bowel disease requires the NLRP3 inflammasome and IL-18. Inflamm Bowel Dis 2015; 21:854-61; PMID:25742401; http://dx.doi.org/10.1097/MIB.0000000000000318

138. Vo HD, Goli S, Gill R, Anderson V, Stefanov DG, Xu J, Kulsum-Mecci N, Schwarz SM, Rabinowitz SS. Inverse correlation between Helicobacter pylori colonization and obesity in a cohort of inner city children. Helicobacter 2015; 20:64-8; PMID:25308209; http://dx.doi.org/10.1111/hel.12154

139. Lender N, Talley NJ, Enck P, Haag S, Zipfel S, Morrison M, Holtmann GJ. Review article: Associations between Helicobacter pylori and obesity—an ecological study. Aliment Pharmacol Ther 2014; 40:24-31; PMID:24832176; http://dx.doi.org/10.1111/apt.12790

140. Cho I, Blaser MJ, Francois F, Mathew JP, Ye XY, Goldberg JD, Bini EJ. Helicobacter pylori and overweight status in the United States: data from the Third National Health and Nutrition Examination Survey. Am J Epidemiol 2005; 162:979-84; PMID:16093294; http://dx.doi.org/10.1093/aje/kwi237

141. Papamichael K, Konstantopouls P, Mantzaris GJ. Helicobacter pylori infection and inflammatory bowel disease: is there a link? World J Gastroenterol 2014; 20:6374-85; PMID:24914359; http://dx.doi.org/10.3748/wjg.v20.i21.6374

142. Thia KT, Loftus EV, Sandborn WJ, Yang SK. An update on the epidemiology of inflammatory bowel disease in Asia. Am J Gastroenterol 2008; 103:3167-82; PMID:19086963; http://dx.doi.org/10.1111/j.1572-0241.2008.02158.x

143. Robinson K, Kenefec R, Pidgeon EL, Shakib S, Patel S, Polson RJ, Zaitoun AM, Atherton JC. Helicobacter pylori-induced peptic ulcer disease is associated with inadequate regulatory T cell responses. Gut 2008; 57:1375-85; PMID:18467372; http://dx.doi.org/10.1136/gut.2007.137539

144. Wagtmans MJ, Witte AM, Taylor DR, Biemond I, Veenendaal RA, Verspaget HW, Lamers CB, van Hogezand RA. Low seroprevalence of Helicobacter pylori antibodies in historical sera of patients with Crohn’s disease. Scand J Gastroenterol 1997; 32:712-8; PMID:9246713; http://dx.doi.org/10.3109/03365529708996523