

Differential inflammatory response to *Helicobacter pylori* infection: etiology and clinical outcomes

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Abstract: The bacterial pathogen *Helicobacter pylori* commonly colonizes the human gastric mucosa during early childhood and persists throughout life. The organism has evolved multiple mechanisms for evading clearance by the immune system and, despite inducing inflammation in the stomach, the majority of infections are asymptomatic. *H. pylori* is the leading cause of peptic ulcer disease and gastric cancer. However, disease outcomes are related to the pattern and severity of chronic inflammation in the gastric mucosa, which in turn is influenced by both bacterial and host factors. Despite over 2 decades of intensive research, there remains an incomplete understanding of the circumstances leading to disease development, due to the fascinating complexity of the host–pathogen interactions. There is accumulating data concerning the virulence factors associated with increased risk of disease, and the majority of these have pro-inflammatory activities. Despite this, only a small proportion of those infected with virulent strains develop disease. Several *H. pylori* virulence factors have multiple effects on different cell types, including the induction of pro- and anti-inflammatory, immune stimulatory, and immune modulatory responses. The expression of multiple virulence factors is also often linked, making it difficult to assess the meaning of their effects in isolation. Overall, *H. pylori* is thought to usually modulate inflammation and limit acute damage to the mucosa, enabling the bacteria to persist. If this delicate balance is disturbed, disease may then develop.

Keywords: *Helicobacter pylori*, inflammation, mucosal immunity, peptic ulcer disease, gastric cancer

Introduction

Barry Marshall and Robin Warren were the first to isolate a spiral bacterium, now known as *Helicobacter pylori*, from inflamed mucosal tissue of the human stomach.¹ In most cases, the infection is asymptomatic. The severity and type of disease depend on the characteristics of the colonizing strain and how it interacts with the host to cause chronic inflammation. Many of the main *H. pylori* virulence factors have multiple effects on different cell types and may have both pro- and anti-inflammatory activities. It is therefore necessary to assess the relative importance and net effects of these factors in order to understand the circumstances leading to disease development.

H. pylori infection

H. pylori has coevolved with humans over the last 60,000 years.² It typically first colonizes the gastric mucosa during early childhood and persists lifelong in the absence of effective eradication treatment.³ It is estimated that approximately 50% of the world's population is colonized, although the prevalence differs between countries.

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Developing countries have a much higher infection rate than developed countries, and this is thought to be due to differences in living conditions and the use of antibiotics, especially in childhood.⁴ Globally, *H. pylori* prevalence is declining. In the US, approximately 10% of individuals under the age of 20 are infected compared to 40% over 60 years of age.⁵ This higher rate of *H. pylori* infection seen with increasing age is not due to acquisition of the infection at a later age, but a birth cohort effect.

H. pylori is found almost exclusively in humans. Other *Helicobacter* species are occasionally found in humans and these are thought to be acquired from domestic pets. The exact route of infectious transmission is not clear, but person-to-person transmission is likely to be a combination of fecal–oral and oral–oral routes. *H. pylori* strains are usually isolated from gastric biopsy tissue, but it is also possible for the bacterium to be isolated from saliva, gastric reflux fluid, and vomitus.⁶

Consequences of *H. pylori* infection

Acute infection

Acute infectious symptoms (such as nausea, halitosis, dyspepsia, and malaise) are experienced by most infected adults but the symptoms are variable. These tend to resolve within 2 weeks. Supporting evidence for the above is mainly from cases of deliberate ingestion. When examined histologically, acute infection is accompanied by severe gastritis, characterized by infiltration of neutrophils and inflammatory cells with marked persistent lymphocyte penetration. A reduction in stomach acid secretion also occurs simultaneously.⁷ It is unknown whether children suffer similar symptoms or whether histological features are concordant.⁸

Chronic infection and disease outcome

Chronic *H. pylori* infection leads to local inflammation of the gastric mucosa (gastritis). Disease risk increases with the level of inflammation, but the pattern of inflammation determines the disease outcome. Host genetic factors, bacterial virulence, environmental factors, and age of infection all influence the distribution of resulting gastritis.⁸ These complex and only partially understood interactions are thought to explain why only 15% of infected individuals develop disease in their lifetime.⁹

The most common and serious complications of *H. pylori* infection include peptic ulcer disease, distal gastric adenocarcinoma, and primary gastric mucosa associated lymphoid tissue (MALT) lymphoma. Other conditions associated with *H. pylori* infection include dyspepsia,

atrophic gastritis, iron deficiency anemia, and idiopathic thrombocytopenia purpura. In contrast, epidemiological evidence also suggests a protective association between *H. pylori* infection and disorders such as gastroesophageal reflux disease (GERD), esophageal adenocarcinoma, inflammatory bowel disease, multiple sclerosis, and asthma.^{10,11}

Peptic ulceration

Peptic ulcers are breaks in the lining of the duodenal or gastric mucosa, most commonly caused by *H. pylori* and nonsteroidal anti-inflammatory drugs. Peptic ulcer disease is associated with significant mortality and complications include hemorrhage and perforation. *H. pylori* eradication heals existing ulcers and prevents their recurrence.¹²

H. pylori is the causative agent in over 75% of duodenal ulcer cases. Antral-predominant inflammation leads to increased gastric acid output (Figure 1). Gastric metaplasia of the duodenal epithelium then permits *H. pylori* to colonize and cause inflammation, which may lead to duodenal ulceration. *H. pylori* is also the leading cause of gastric ulcers, which develop in patients with pangastritis. Here the acid output is normal or reduced, thus preventing the development of duodenal ulcers, but gastric ulcers may develop. Premalignant lesions and gastric adenocarcinoma may also arise.^{2,13,14}

Gastric adenocarcinoma

Gastric cancer is ranked the fifth most common malignancy worldwide with an estimated 100,000 new cases per year.¹⁵ Most cases are found in Asia, with over two-thirds occurring in the People's Republic of China.¹⁶ Gastric cancer is the third most common cause of cancer-related deaths, since initial diagnosis is usually at a late stage.^{17,18} It can be divided into two subtypes depending on the location: cardia (arising from the gastroesophageal junction) and noncardia (arising from the distal stomach). Cardia gastric cancers share risk factors with esophageal adenocarcinoma, Barrett's esophagus, obesity, and GERD.¹⁵ Noncardia gastric cancer is strongly associated with *H. pylori*, and it is thought that up to 89% may be attributed to the infection. Thus *H. pylori* has been classified as a human carcinogen.¹⁹ The lifetime risk of an *H. pylori*-infected individual developing gastric cancer is 1%–2%.^{14,20}

There are two histological types of gastric adenocarcinoma: intestinal and diffuse. The intestinal type develops gradually, following a stepwise progression driven by inflammation. *H. pylori* infection of the normal gastric mucosa leads to a state of chronic gastritis, which later leads to atrophic gastritis (characterized by gland loss and infiltration of inflammatory cells), intestinal metaplasia (where gastric epithelial cells are replaced

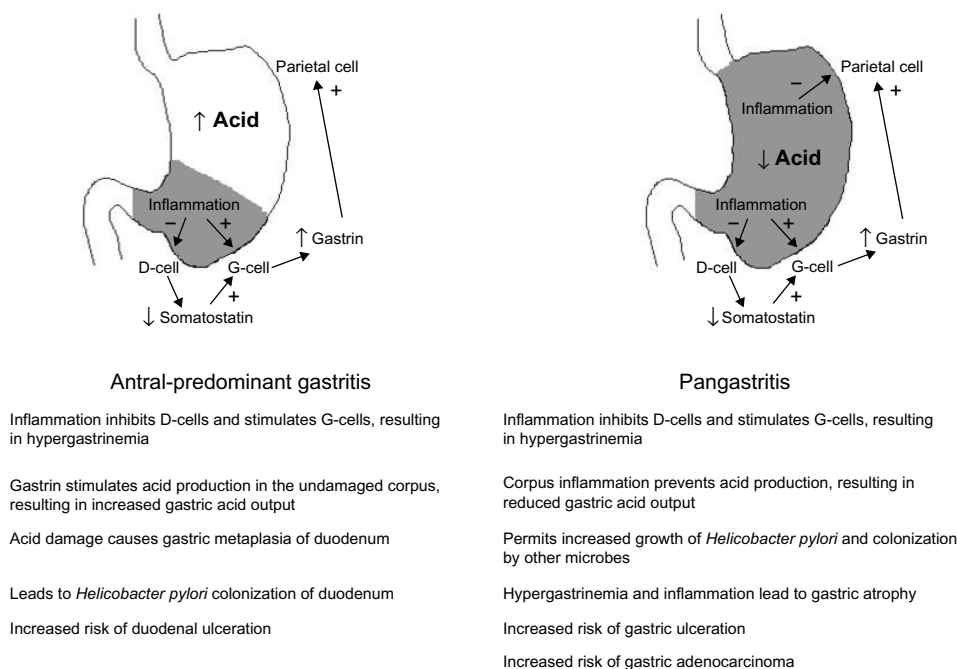


Figure 1 The effect of gastritis pattern on gastric acid production and associations with duodenal and gastric disease.

with those of an intestinal type), dysplasia (neoplasia confined to epithelial cells), and finally adenocarcinoma.²¹ The diffuse type usually affects younger patients and is not associated with intestinal metaplasia. Although thought to be triggered by *H. pylori* infection, the exact mechanism is not known.¹⁷ *H. pylori* eradication has been shown to reduce the incidence of atrophic gastritis but does not result in a reduction in gastric cancer incidence unless achieved before the appearance of premalignant changes.²²

MALT lymphoma

H. pylori colonization is strongly linked to MALT lymphoma.²³ Due to the rarity of this condition, the exact number of individuals coinfecting with *H. pylori* is not known but the condition occurs in less than 1% of those who are colonized. Low-grade B-cell MALT lymphomas normally regress following *H. pylori* eradication treatment.²⁴

Host response to *H. pylori* and its association with disease risk

H. pylori elicits a strong immune response, stimulating the expression of cytokines and chemokines from gastric epithelial cells. These factors attract neutrophils, macrophages, dendritic cells (DCs), natural killer (NK) cells, and lymphocytes,^{8,25} and induce the release of reactive oxygen species (ROS) and reactive nitrogen species (RNS). Gastric carcinogenesis is associated with ROS/RNS-mediated DNA damage, silencing

of tumor suppressor genes via DNA methylation, histone epigenetic modification, and epithelial–mesenchymal transition.²⁶ The level and nature of the immune response varies and this affects the risk of disease development.²⁷

Interactions of *H. pylori* with gastric epithelium

The surface of the gastric mucosa is covered by protective mucus consisting of a cell-associated layer (predominantly MUC1) and secreted mucin (mainly MUC5AC).²⁸ This layer has a profound impact on *H. pylori* adhesion to the gastric mucosa. *H. pylori* interacts with mucin fucosylated Lewis^b blood group antigen moieties via the BabA adhesin.²⁹ During gastritis, there is an increase in sialylated mucin structures such as sialyl-Lewis^x and sialyl-Lewis^a, and these bind to the adhesin SabA.³⁰ Recently, the LabA adhesin was identified as binding a motif on MUC5AC.³¹ The mucus layer is also important for *H. pylori* motility; the organism reduces its viscosity in order to move through it.³² Mucins also have natural antibiotic activity against the bacterium,³³ and *H. pylori* binding to MUC1 induces multiple effects on host cells including the modulation of inflammation.³⁴

Innate immunity and inflammation

Pattern recognition receptors (PRRs) expressed by gastric epithelial cells interact with *H. pylori* and activate inflammatory gene expression. These molecules, which

include the toll-like receptors (TLRs) and nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), recognize pathogen-associated molecular patterns (PAMPs) such as lipopolysaccharide (LPS), flagellins, and cell wall peptides.³⁵ Some *H. pylori* PAMPs are modified to weakly activate PRRs, since its tetra-acetylated LPS is poorly recognized by *TLR4*, and the FlaA flagellin binds much less efficiently to *TLR5*.³⁶ Unlike other bacteria, *TLR2* appears

to be the main receptor for *H. pylori* LPS, but *TLR2* is also activated by other components (Table 1).³⁷ Polymorphisms in *TLR1*, *TLR2*, *TLR4*, *TLR5*, and *TLR9* genes have been associated with more severe gastritis and increased risk of premalignant pathology.^{38,39}

Interaction of the cytotoxin-associated gene pathogenicity island (*cagPAI*) encoded type IV secretion system (T4SS) with gastric epithelial cells results in the transfer of soluble

Table 1 Major virulence factors and their effects on inflammation and the immune response

| Virulence factor | Pro-inflammatory roles | Anti-inflammatory roles |
|--|---|---|
| CagA and the <i>cagPAI</i> -encoded type IV secretion system | Stimulates NF- κ B activation in gastric epithelial cells, leading to expression of pro-inflammatory cytokines and chemokines; activation of MAPK signaling, leading to cell proliferation and inflammatory gene expression; disruption of epithelial cell junctions | CagA induces cell cycle arrest in T-cells; <i>cagPAI</i> -mediated signaling downregulates the expression of pro-inflammatory hBD1 |
| VacA | Induction or dysregulation of autophagy; induces IL-8 production by monocytes and macrophages via p38 MAPK signaling; activates mast cells and induces inflammatory cytokine expression; plays a role in maintaining colonization | Binds CD18 on human T-cells and directly inhibits the activation and proliferation of human B and T lymphocytes; exerts tolerizing effects on DCs to stimulate a Treg response; inhibits antigen presentation; inhibits DC maturation via effects on E2F1 signaling; induces T-cells to express the Treg transcription factor Foxp3 |
| DupA and the <i>tfs4</i> -encoded type IV secretion system | Induction of pro-inflammatory cytokine secretion by monocytes and epithelial cells | None reported |
| HP-NAP | Activates neutrophils and induces ROS; stimulates <i>TLR2</i> ; stimulates macrophages to produce IL-12 and IL-23; induces IL-6 production by mast cells; inhibits Th2 responses and promotes the development of a Th1 response | None reported |
| Heat shock protein 60 | Interacts with <i>TLR2</i> ; stimulates macrophages and induces IL-12 and IL-23 expression | Induces a strong IL-10 response from human peripheral blood mononuclear cells |
| OipA | Mediates closer interaction with gastric epithelium and induces pro-inflammatory cytokine expression; reduces IL-10 production by DCs; disruption of epithelial cell tight junctions (with <i>cagPAI</i> signaling) | Inhibits DC maturation and promotes the differentiation of naïve T-cells into Tregs |
| Peptidyl prolyl cis-, transisomerase (HP0175) | Interacts with <i>TLR4</i> ; stimulates a Th17 response | None reported |
| Fucosylated Lewis blood group antigens (LPS moieties) | Interact with major adhesins; mediate closer interaction and exposure of epithelial cells to <i>H. pylori</i> virulence factors | Interaction with DC-SIGN on DCs to increase IL-10 expression and suppress IL-6; modulation of Th1/Th2 balance |
| SabA | Interacts with sialylated receptors on neutrophils to induce ROS production; mediates closer interaction and exposure of epithelial cells to <i>H. pylori</i> virulence factors | None reported |
| Gamma-glutamyl transpeptidase | Induces NF- κ B activation, IL-8 production, and ROS by gastric epithelial cells; gastric epithelial cell death; stimulates a Th17 response | Potent T-cell suppressant activity; induces T-cells to express the Treg transcription factor Foxp3; upregulates COX2 expression in T-cells which modulates Th1 response |

Abbreviations: IL, interleukin; DC, dendritic cell; *H. pylori*, *Helicobacter pylori*; ROS, reactive oxygen species; TLR, toll-like receptor; Th, T-helper; LPS, lipopolysaccharide; NAP, neutrophil-activating protein.

peptidoglycan components into the cytoplasm, NOD1 activation, and pro-inflammatory gene expression.⁴⁰ The largest NLR subfamily includes the NLRPs, which are the scaffolding proteins of inflammasomes. NLRPs interact with adaptor proteins leading to the activation of caspase-1, which controls the maturation of inflammatory cytokines such as IL-1 β and IL-18.⁴¹ There is increased expression of these factors and other NLRP3-related molecules in infected gastric tissue.^{39,42}

Autophagy, the pathway for breakdown and removal of damaged cellular components, is an important homeostatic mechanism which regulates inflammatory signaling.⁴³ Dysregulation of autophagy has been reported to result in increased production of ROS and DNA damage. This leads to accumulations of damaged organelles, changes in cell metabolism, and carcinogenesis.⁴⁴ *H. pylori*-mediated induction of autophagy has been reported;^{45,46} however, more virulent *H. pylori* isolates rapidly downregulate autophagy in gastric epithelial and monocytic cells lines.⁴⁷ Characterization of the *H. pylori* B128 7.13 strain, which causes gastric cancer in Mongolian gerbils, revealed a mutation in a peptidoglycan deacetylase gene (*pgdA*). This led to reduced autophagy in vitro and cancer development in animals.⁴⁸

Secreted antimicrobial peptides are produced in response to *H. pylori*. Elevated levels of human beta defensin 2 (hBD2), hBD3, hBD4, adrenomedullin, angiogenin, alpha defensins 1, 2, and 3, and the human cationic antimicrobial peptide 18 (LL-37) are present in the gastric mucosa of *H. pylori*-infected patients and/or infected human gastric epithelial cells in vitro.^{49–54}

As a consequence of *H. pylori* interactions with the epithelium, pro-inflammatory chemokines and cytokines, including IL-8, IL-1 β , tumor necrosis factor alpha (TNF α), IL-6, IL-12, CCL2-5, CCL20, and CXCL1-3, are upregulated in the infected gastric mucosa.^{55,56} Gene polymorphisms resulting in increased expression of pro-inflammatory cytokines (IL-6, IL-8, TNF α , IL-1 β), or reduced expression of anti-inflammatory cytokines (IL-10), are associated with higher risk of disease.^{27,57,58} The presence of chemokines leads to the recruitment of immune cells, including neutrophils, macrophages, DCs, NK cells, and lymphocytes.² Neutrophils contribute to gastritis by secreting inflammatory cytokines and releasing tissue damaging factors from neutrophilic granules. They also phagocytose bacteria, and within the phagolysosomes the bacteria are exposed to bactericidal factors, including myeloperoxidase and matrix metalloproteinases which degrade cell walls and proteins, and ROS and RNS, which induce DNA damage. *H. pylori* prevents the oxidative

burst and can survive intracellularly within neutrophils.⁵⁹ *Helicobacter*-infected neutrophil-depleted mice appear to be colonized at the same densities as normal mice.⁶⁰ These data imply that neutrophils may play a lesser role in protective immunity, but contribute to mucosal damage.

Macrophage-depleted mice have a significantly reduced *H. pylori* gastritis severity.⁶¹ Both M1 and M2 macrophages are present in the infected gastric mucosa.⁶² M1 macrophages secrete pro-inflammatory cytokines and nitric oxide and have potent bactericidal activity compared with M2 macrophages, which promote cell proliferation and tissue repair.⁶³ *H. pylori* is able to survive phagocytosis by macrophages, since it induces the fusing together of phagosomes to form megasomes without lysosomal fusion.⁶⁴ The megasomes provide a protected intracellular niche and may even contribute to the persistence of infection.⁶⁵ *H. pylori* is also able to neutralize the released ROS via catalase activity, and arginase production by the bacteria inhibits nitric oxide production.^{66,67} Chronic exposure to ROS and RNS, however, results in host cell DNA damage and favors cancer development.

Mast cells are also present at higher frequencies in the *H. pylori*-infected human gastric mucosa.⁶⁸ The role of these cells has not been widely studied, but they may be involved in tissue repair, inflammation, and vaccine-mediated clearance of the infection.⁶⁹

DCs in *H. pylori*-infected gastric tissue tend to be of a myeloid type (mDCs) and express DC-SIGN and high levels of HLA-DR, but are semi-mature and tolerogenic.^{70–75} Together with the DC response, macrophage-derived cytokines also have an important influence on the development and balance of the adaptive immune response.⁷⁶ It has recently been shown that both human gastric epithelial cells and gastric mucosal DCs produce retinoic acid (RA), an important factor that regulates inflammation. When infected with *H. pylori*, however, mucosal RA production is impaired, leading to increased inflammation and possibly resulting in increased risk of peptic ulceration and gastric carcinogenesis.⁷⁷

Despite recent interest in invariant lymphoid and NK cell populations there is very little data on these in the context of *H. pylori* infection. NKT cells are more abundant in the infected gastric mucosa, and a larger NK cell population was detected in the peripheral blood of infected donors.^{78,79} How these cell types contribute to disease is not understood; however, NK cell-derived perforin and granzymes may cause damage to host cells. NK cells respond to incubation with *H. pylori* or its secreted products by secreting inflammatory cytokines such as interferon-gamma (IFN γ) and TNF α .⁸⁰

Adaptive immunity

Strong IgG and IgA antibody responses are present in *H. pylori*-infected individuals and these may trigger autoimmunity.⁶⁶ Molecular mimicry by *H. pylori* induces antibodies that react with host antigens in the gastric mucosa, such as the parietal cell H⁺, K⁺-ATPase.⁸¹ Such autoreactive antibodies are frequently present in the serum of infected patients, and these may increase local inflammation and damage in the stomach or elsewhere.⁸²

H. pylori infection induces a vigorous T-cell response, which includes both CD4⁺ and CD8⁺ cells. The gastric mucosa of infected humans and mice contains increased numbers of CD8⁺ cells and these contribute to inflammation and disease.⁸³ More is known about the CD4⁺ T-helper (Th) response. The main Th subsets induced by *H. pylori* infection are pro-inflammatory Th17 and Th1 and anti-inflammatory regulatory T-cell (Treg) populations; however, Th2 and Th22 responses have also been reported.^{84–88} Th-derived cytokines orchestrate the host response, having an impact on *H. pylori*-induced inflammation and immunity, as well as playing an important role in determining *H. pylori*-associated disease risk.

Th1 cells secrete cytokines IFN γ and TNF α , which stimulate macrophages to secrete further pro-inflammatory factors and have more bactericidal activity.⁸⁹ Th17 cells secrete IL-17A, IL-17F, IL-21, and IL-22, and stimulate the expression of antimicrobial peptides, ROS, RNS, and chemokines. This leads to increased inflammation and neutrophil recruitment.⁹⁰ *H. pylori*-induced expression of B-cell activating factor of TNF family (BAFF) by macrophages is important for the differentiation of Th17 cells.⁷⁶ In *H. pylori*-infected mice, a Th17 response is observed in addition to the Th1 response, leading to more severe gastritis.⁹¹

In the infected human and mouse gastric mucosa, the severity of gastritis correlates with the number of Th1 and Th17 cells.^{92–94} Although a strong Th1 response may contribute to carcinogenesis, there is evidence that a high Th1 response leads to a better prognosis for gastric cancer patients due to stronger antitumor immunity.⁹⁵ On the other hand, high-level Th17 and Th22 responses are associated with gastric cancer progression and poor survival, possibly due to the role of their cytokines in angiogenesis and tumor invasiveness.⁹⁶ Gastric Th1 cells from the antrum of patients with peptic ulcer disease provide help for B-cell antibody isotype switching, induce epithelial cells to express higher levels of MHC class II, and also have *H. pylori*-specific cytolytic activity.⁹⁴ They are proposed to contribute to disease via cytotoxicity against antigen-presenting epithelial cells, and may

also promote autoimmune reactions such as in autoimmune gastritis and gastric MALT lymphoma.^{81,94} T-cell clones from patients with MALT lymphoma, however, are commonly Th0 rather than Th1 types. These have a markedly reduced cytotoxic activity against B-cells and an impaired ability to induce apoptosis in T-cells. This may explain the unchecked B-cell expansion in MALT lymphoma.⁹⁷

H. pylori has multiple mechanisms for directing the immune system away from a pro-inflammatory T-cell response and toward a suppressive Treg response.⁹⁸ Increased numbers of Tregs are observed in the gastric mucosa and peripheral blood of *H. pylori*-infected patients, and peptic ulceration is more frequently found in those with reduced Treg numbers in their gastric mucosa.^{56,84,92,99} Tregs may act by secreting cytokines such as IL-10 and transforming growth factor beta to modulate inflammation, or they may act via contact-mediated mechanisms.¹⁰⁰ *H. pylori* influences DCs to promote the differentiation of naïve T-cells into Tregs. Such responses are reported to protect against extra-gastric immune and inflammatory conditions including asthma and inflammatory bowel disease.^{74,101}

In addition to Treg induction, *H. pylori* utilizes many other mechanisms to modulate the immune and inflammatory response. Several virulence factors have anti- as well as pro-inflammatory functions (Table 1), and expression of B7-H1 is upregulated in gastric epithelial cells during *H. pylori* infection. Interaction with this molecule suppresses T-cell activity.¹⁰²

Virulence factors and inflammation

H. pylori produces numerous virulence factors, many of which are highly polymorphic, phase variable, genetically linked, and/or have diverse and sometimes opposing functions. This diversity, together with the complexity of the host immune response, makes it difficult to define clearly the relative roles of individual virulence factors in *H. pylori*-mediated inflammation and disease. Pro- and anti-inflammatory influences of some of the best-studied *H. pylori* virulence factors are briefly summarized in this section.

The *cag* pathogenicity island and CagA

The *cagPAI* is a 40 kb horizontally transmitted segment of DNA. It encodes a T4SS, with CagL at the tip of the needle-like structure which binds to $\alpha 5\beta 1$ integrin on host cells.¹⁰³ CagA, an immunodominant 120–145 kDa protein, is injected into cells through the T4SS together with peptidoglycan peptides. This process activates NF- κ B, triggering the secretion of pro-inflammatory cytokines and chemokines, most notably

IL-8. Once inside the host cell, CagA is rapidly tyrosine phosphorylated at its EPIYA (Glu-Pro-Ile-Tyr-Ala) motifs by Src kinases and then interacts with the SHP-2 cellular phosphatase. This ultimately leads to cytoskeletal changes via actin rearrangement.¹⁰⁴ Unphosphorylated CagA also interacts with numerous targets inside the host cell including the tight junction protein ZO-1 (causing tight junction disruption) and E-cadherin (disrupting E-cadherin/ β -catenin complexes to promote β -catenin mediated upregulation of genes with oncogenic potential).^{105,106} Taken together, *cagPAI* activity drives a scattering/elongation, or “hummingbird”, phenotype and pro-inflammatory responses in gastric epithelial cells. However, *cagPAI*-mediated NF- κ B activation also downregulates the expression of the antimicrobial and pro-inflammatory defensin hBD1, and the activation of SHP-2 by CagA prevents EGFR-mediated expression of hBD-3.^{53,107} Downregulation of these β -defensins may help promote the persistence of CagA-positive *H. pylori* strains.

The *cagPAI* may be present fully, partially, or not at all. Strains with a functional *cag* T4SS are strongly associated with increased gastric cancer risk. The *cagA* gene sequence is itself polymorphic. EPIYA motifs may be categorized as EPIYA-A, B, C, or D depending on their flanking sequences, with EPIYA-A, B, and C found in Western CagA types and EPIYA-A, B, and D found in East Asian CagA. A larger number of EPIYA-C motifs or the presence of an EPIYA-D increases interactions with SHP-2, and is associated with a higher risk of intestinal metaplasia and gastric cancer.¹⁰⁸ Strains lacking CagA may induce inflammation via other *cagPAI*-dependent mechanisms. If the T4SS is functional, peptidoglycan peptides enter the cell and activate NOD1-mediated signaling.⁴⁰ Additionally, interaction of CagL with the α 5 β 1 integrin is sufficient to activate NF- κ B and induce IL-8 expression.¹⁰⁹

Vacuolating cytotoxin (VacA)

Virtually all *H. pylori* strains possess the *vacA* gene but it is highly polymorphic, with two alternative allelic variants for the signal (s1/s2), intermediate (i1/i2), and mid- (m1/m2) regions. The mid-region plays a role in host cell binding, and m1 forms are able to bind a wider range of cell types than m2. s2 and i2 VacA have reduced activity compared to the s1 and i1 variants.^{110,111} VacA is a pore-forming toxin, originally named for its ability to induce vacuolation in gastric epithelial cells in vitro. A myriad of other functions have also been attributed to it, including the induction of epithelial cell apoptosis, autophagy, and inhibition of T-cell activation (Table 1).^{46,112,113}

The *vacA* s1 and i1 alleles are associated with increased risk of peptic ulceration, atrophy, and gastric adenocarcinoma, but genetic linkage between these alleles and the presence of *cagA* makes it difficult to determine with certainty the contribution of each individual factor.¹¹¹ There is also functional linkage between VacA and CagA, for example, VacA induces apoptosis in gastric epithelial cells, but CagA blocks this activity and can also prevent VacA gaining access into host cells.^{114,115} This may protect the host cell to which the bacterium has adhered, while allowing continued VacA-mediated disruption of more distant cells. Conversely, VacA inhibits the induction of the hummingbird phenotype by CagA.¹¹⁶ Recently, VacA and another secreted *H. pylori* protein, γ -glutamyl transferase have been shown to tolerize DCs, promoting Treg responses and protecting against asthma in a mouse model.^{117,118} Since both s1i1m1 and s2i2m2 VacA can tolerize DCs, this anti-inflammatory function may be one reason for the otherwise unexplained maintenance of apparently nonfunctional type 2 toxin variants in the *H. pylori* genome.

DupA and *tfs4*

H. pylori genomes contain regions of low GC content and high diversity, known as “plasticity zones”. The number and contents of PZs vary between strains, and several PZ-specific genes are associated with disease. Of these, one of the best studied is the duodenal ulcer-promoting gene, *dupA*. The *tfs4* gene cluster comprises *dupA* and other *vir* homologues which are thought to encode a type IV secretion system.¹¹⁹

Although *dupA* was initially identified as a duodenal ulcer-promoting virulence factor, numerous subsequent conflicting studies have left the role of *dupA* in disease unclear. This is likely due to the requirement for other components of the *tfs4* to produce a functional type IV secretion system, making *dupA* alone an imperfect marker.^{120,121} The presence of *dupA* in clinical *H. pylori* isolates is associated with increased IL-8 levels in the antrum of infected individuals.^{122,123}

H. pylori neutrophil-activating protein (HP-NAP)

HP-NAP is a highly conserved dodecameric 150 kDa protein, named for its ability to stimulate endothelial adhesion and production of oxygen radicals by neutrophils. The protein is also a neutrophil chemottractant and stimulates these cells to produce pro-inflammatory cytokines and chemokines. Since neutrophil infiltration is a dominant characteristic of *H. pylori* gastritis, HP-NAP may play a central role in *H. pylori*-associated disease. HP-NAP may also associate with

the outer membrane of intact bacteria and play a role in binding to host mucin carbohydrates.^{124,125}

Adhesins

Adherent bacteria might be expected to induce stronger inflammatory responses than nonadherent bacteria. *H. pylori* possesses several major adhesins including the blood group antigen binding adhesin (BabA), sialic acid binding adhesin (SabA), and OipA.

BabA is expressed by a subset of *H. pylori* strains, and it binds to difucosylated Le^b blood group antigens on host epithelial cells.²⁹ BabA may facilitate close association with the epithelium for delivery of other virulence factors, and indeed *babA2*-positive strains are associated with increased gastric mucosal granulocyte infiltration and IL-8 expression.¹²⁶

sabA is a phase-variable gene that may be switched “on” or “off”. SabA allows *H. pylori* to adhere to sialylated Lewis antigens, which are present during gastritis.³⁰ BabA plays the major role in bacterial adhesion soon after colonization, and SabA becomes the predominant adhesin once chronic inflammation is established. Colonization with SabA-producing strains is associated with increased risk of gastric cancer, atrophy, and intestinal metaplasia; however, there is a negative association between SabA expression and neutrophil infiltration.¹²⁷

OipA is another phase-variable adhesin, and it has several other putative functions including the induction of actin stress fiber formation and IL-8 production by epithelial cells. OipA shares some activities and host cell signaling pathways with the *cagPAI*, and IL-8 expression may be induced synergistically. There is also OipA-specific signaling, however. While “on” OipA is associated with increased risk of duodenal ulcer and gastric cancer, defining the relative roles of *cagPAI* and *oipA* is not straightforward because *oipA* “on” strains are also likely to be *cagPAI*-positive.^{128,129}

Conclusion

H. pylori infection strongly stimulates gastric mucosal inflammation and both the innate and acquired immune response. The usual consequence of *H. pylori* infection is chronic asymptomatic gastritis, probably because the bacteria have adapted to evade and suppress the immune response. The inflammatory response is important in the development of gastric adenocarcinoma; however, there is growing evidence that other aspects of the local and systemic response are also central to disease pathogenesis. It may ultimately be possible to develop prognostic tests based on these parameters, along with bacterial virulence types, to predict

who is at risk of developing gastric cancer. However, since many of the major virulence factors have both pro- and anti-inflammatory activities, further research is necessary to gain a complete understanding of the circumstances leading to disease occurrence.

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The authors report no conflicts of interest in this work.

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