Immune responses to *Helicobacter pylori* colonization: mechanisms and clinical outcomes

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**ABSTRACT**

*Helicobacter pylori* colonizes the stomachs of half of the world’s population and usually persists in the gastric mucosa of human hosts for decades or life. Although most *H. pylori*-positive people are asymptomatic, the presence of *H. pylori* is associated with increased risk for the development of peptic ulcer disease, gastric adenocarcinoma and gastric lymphoma. The development of a sustained gastric inflammatory and immune response to infection appears to be pivotal for the development of disease. During its long co-existence with humans, *H. pylori* has evolved complex strategies to maintain a mild inflammation of the gastric epithelium while limiting the extent of immune effector activity. In this review, the nature of the host immune response to *H. pylori* infection and the mechanism employed by the bacterium to evade them is considered. Understanding the mechanisms of colonization, persistence and virulence factors of the bacterium as well as the innate and adaptive immune responses of the host are critically important for the development of new strategies to prevent the development of *H. pylori*-induced gastroduodenal disease.

**INTRODUCTION**

*Helicobacter pylori* is a Gram-negative microaerophilic spiral bacterium that colonizes the gastrointestinal mucosa of its host and, despite a strong persistent humoral and cellular immune response to *H. pylori* at the local and systemic level, the organism persists for the lifetime of its host. Virtually all people carrying *H. pylori* have co-existing gastric inflammation; however, only a small percentage of colonized individuals develop clinically apparent sequelae.

Chronic gastritis induced by *H. pylori* increases the risk for a wide spectrum of clinical outcomes, ranging from peptic ulcer disease (gastric and duodenal ulceration) to distal gastric adenocarcinoma and gastric mucosal lymphoproliferative diseases, such as non-Hodgkin’s lymphoma [1]. Although the factors determining the variable outcome of *H. pylori* infection are not well understood, the development of a sustained gastric inflammatory and immune response to infection appears to be pivotal for the development of disease. Enhanced risk may be related to differences in the expression of specific bacterial products, to variations in the host inflammatory response to the bacteria or to specific interactions between host and microbe [2].

We are only now beginning to understand the bacterial and host factors that are involved in the host–pathogen interaction during persistent colonization with *H. pylori*. The answers to these questions are likely to provide new and exciting directions for research in the fields of...

**Key words:** colonization, gastric mucosa, *Helicobacter pylori*, immune response, inflammation.

**Abbreviations:** APC, antigen-presenting cell; CI, confidence intervals; DC, dendritic cell; HcpA, *Helicobacter* cysteine-rich protein A; IFN-γ, interferon-γ; IL, interleukin; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor κB; NO, nitric oxide; PAI, pathogenicity island; sIgA, secretory IgA; TLR, Toll-like receptor; TNF-α, tumour necrosis factor-α; Treg, CD4+CD25+ regulatory T-cells.

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microbial pathogenesis and immunology. This review focuses on the immune response to *H. pylori* colonization and its effect on clinical outcomes.

**EPIDEMIOLOGY**

*H. pylori* is the most common chronic bacterial infection in humans [3]. Infection with *H. pylori* occurs worldwide, but the prevalence varies greatly among countries and among population groups within the same country. 

*H. pylori* colonizes the stomachs of 50% of the population in developed countries and approx. 80% in the developing world. The infection is acquired by oral ingestion of the bacterium and is mainly transmitted within families. The main source of transmission is the mother within families [4]. Acquisition of *H. pylori* apparently takes place in early childhood and is rare or does not occur in adults. In industrialized countries, the rate of acquisition of *H. pylori* has decreased substantially over recent decades. Therefore the continuous increase in prevalence of *H. pylori* with age is due mostly to a cohort effect, reflecting more intense transmission at the time when members of earlier birth cohorts were children [5]. The organisms can be cultured from vomitus or diarrhoeal stools, suggesting the potential for transmission among family members during periods of illness [6].

The overall prevalence of *H. pylori* is strongly correlated with socioeconomic conditions. Factors such as density of housing, overcrowding, number of siblings, birth order, sharing a bed and lack of running water have all been linked to a higher acquisition of *H. pylori* infection [7].

**PATHOGENESIS**

**Colonization of the gastric mucosa**

Gastric acidity and peristalsis normally inhibit bacterial colonization of the human stomach. However, natural selection has provided *H. pylori* with several mechanisms to elude these primary defences and establish persistent infection, such as the ability to withstand acidic gastric pH and motility (Table 1).

After being ingested, *H. pylori* has to evade the bactericidal activity of the gastric luminal contents and establish intimate contact with the mucous layer. The enzyme urease metabolizes urea to carbon dioxide and ammonia to buffer the gastric acid. Flagella allow the bacterium to swim across the viscous gastric mucus and reach the more neutral pH below the mucus. Knockout *H. pylori* mutants of urease or flagellar genes are defective in gastric colonization in a gnotobiotic piglet model of infection [8,9].

Once below the mucus, *H. pylori* adheres tightly to the underlying cells. The best characterized adhesin, BabA, is a 78 kDa outer-membrane protein that binds to the fucosylated Lewis+b blood-group antigen.

Persistent colonization depends on the ability to respond to changing environmental conditions and circumvent host defence mechanisms initiated during infection. Rearrangement of genomic DNA allows a variety of pathogens to adapt expression of surface antigens and evade host immunity. *H. pylori* has the highest rate of genetic recombination of any known bacterial species, suggesting that this process confers a selective advantage in colonization. Loughlin et al. [10] have shown that *H. pylori* mutants defective for homologous recombination were spontaneously cleared from the murine gastric mucosa, whereas the *H. pylori* wild-type strain established a persistent high level of colonization.

**Virulence factors**

The major disease-associated genetic difference in *H. pylori* isolates is the presence or absence of the cag-PAI (pathogenicity island), a 40 kb genomic fragment containing ORFs (open reading frames) that represent 31 genes. As in other bacterial pathogens, the PAI has been acquired by horizontal transfer of a genetic cassette.

The cag-PAI is present in 60–70% of US clinical strains. A particular cluster of these genes encodes for a type IV bacterial secretion system which, in addition to playing a role in the inflammatory response, has been shown to deliver the immunodominant CagA protein that is encoded in the cag-PAI inside the host cells. Once inside the gastric epithelial cell, CagA is tyrosine phosphorylated by Src kinase activity, leading to a growth-factor-like cellular response and cytokine production by the host cell [11]. Because of these functions, *H. pylori* cagA*+* strains are associated with a significantly increased risk for severe gastritis, atrophic gastritis, peptic

### Table 1  *H. pylori* proteins that may contribute to gastric colonization

<table>
<thead>
<tr>
<th>Product</th>
<th>Gene(s)</th>
<th>Putative functions</th>
<th>Targeted host defence</th>
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<tr>
<td>Urease</td>
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<td>Gastric acid neutralization</td>
<td>Gastric acid</td>
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<tr>
<td>Flagella</td>
<td>flaA, flaB, flaG and flaA</td>
<td>Motility</td>
<td>Gastric peristalsis</td>
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<td>Adhesins</td>
<td>bbaA and others</td>
<td>Adherence to gastric epithelium</td>
<td>Gastric peristalsis</td>
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<tr>
<td>Lewis antigens</td>
<td>galT, futA, futB and futC</td>
<td>Adherence to gastric epithelium</td>
<td>Gastric peristalsis</td>
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<td>? Molecular mimicry</td>
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<td>Humoral immune response</td>
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ulcer disease and distal gastric cancer compared with cagA− strains [12,13].

A second locus of heterogenicity is the gene vacA, which encodes the vacuolating cytotoxin. VacA is a secreted protein toxin that is responsible for the gastric epithelial erosion observed in infected hosts. Despite the fact that 100% of H. pylori strains carry the vacA gene, approx. 50% of H. pylori strains produce a functional VacA protein [14]. H. pylori strains that express vacuolating activity are more common among patients with peptic ulcer disease and distal gastric cancer than among infected patients with superficial gastritis alone [15]. Although vacA is conserved among all H. pylori strains, significant polymorphism exists. vacA alleles possess one of two types of signal region, s1 or s2, and one of two mid-regions, m1 or m2, occurring in all possible combinations. H. pylori strains with different forms of vacA exhibit varied phenotypes and have particular associations with gastroduodenal diseases. vacA s1/m1 strains are most closely associated with gastric carcinoma [16].

HOST RESPONSE TO H. PYLORI

The immune response towards bacterial pathogens can be divided into an innate and an adaptive response. The innate response towards bacterial infection is generally an initial non-specific process, which reacts quickly with several bacterial molecules to signal infectious danger and with the aim of killing the bacteria. By contrast, the adaptive immune response is delayed, antigen-specific, leads to the activation of T-, B- and memory cells and is shaped by the innate immune response.

Innate immunity

Recognition of bacterial molecules by the innate immune system is mediated by TLRs (Toll-like receptors) expressed on APCs (antigen-presenting cells) such as monocytes and DCs (dendritic cells). Bacterial contact with monocytes and other APCs leads to the secretion of pro-inflammatory cytokines such as TNF-α (tumour necrosis factor-α), IL (interleukin)-1β and IL-8. H. pylori infection has been shown to be associated with increased levels of these cytokines which, in turn, act as local chemo-attractants, inducing granulocytic infiltration [17].

Thus far, many of the studies on innate immune responses to H. pylori in epithelial cells have focused on TLR4, the specific ‘pathogen-recognition molecule’ (PRM) of Gram-negative LPS (lipopolysaccharide). However, gastric epithelial cell lines were non-responsive to H. pylori LPS, even when relatively high concentrations of this endotoxin were added to the cells [18]. Consistent with this, a TLR4-neutralizing antibody did not block H. pylori-induced secretion of the pro-inflammatory cytokine IL-8 in AGS cells [19].

Two additional TLRs, TLR2 and TLR5, have been shown to participate actively in innate immune responses to Gram-negative bacteria through their recognition of lipoproteins and flagellin respectively. A role for TLR2 and TLR5 signalling to H. pylori was suggested by a study showing an increase in NF-κB (nuclear factor κB) luciferase reporter activity in H. pylori-stimulated HEK-293 cells that had been co-transfected to express TLR2, TLR4 or TLR5. Infection of the cultures with H. pylori induced NF-κB activity in cells transfected with TLR2 and TLR5, but not TLR4 [20]. Other groups, however, demonstrated that flagellin-responsive epithelial cell lines do not detect native or recombinant H. pylori flagellin, suggesting that H. pylori flagellin evades TLR5 recognition [21].

Several studies have demonstrated that contact between H. pylori and gastric epithelial cells results in a rapid activation of NF-κB, which is followed by increased IL-8 expression [22]. The ability of H. pylori to activate NF-κB in vitro has also been corroborated in vivo as activated NF-κB is present within gastric epithelial cells of infected, but not uninfected, patients, which mirrors the location of increased IL-8 protein within colonized mucosa [23].

In addition to NF-κB, MAPks (mitogen-activated protein kinases) have been implicated as mediators of H. pylori-induced IL-8 expression. In vitro studies utilizing IL-8 reporter constructs have now revealed that H. pylori-induced IL-8 gene expression is dependent upon activation of both NF-κB and AP-1 (via activation of MAPks), indicating that synergistic interactions between AP-1 and NF-κB within the IL-8 promoter are required for maximal H. pylori-induced IL-8 production [24].

Adaptive immunity

Cellular response

Adaptive immune responses towards H. pylori infection have also been identified. H. pylori causes continuous gastric inflammation in virtually all infected people. This inflammatory response initially consists of neutrophils, followed by lymphocytes (T- and B-cells), plasma cells and macrophages, along with varying degrees of epithelial cell degeneration and injury [25].

Since H. pylori rarely, if ever, invades the gastric mucosa, the host response is triggered primarily by the attachment of bacteria to epithelial cells. The organism produces a number of antigenic substances, including HSP (heat-shock protein), urease and LPS, all of which can be taken up and processed by lamina propria macrophages and activate T-cells [26]. Cellular disruption, especially adjacent to epithelial tight junctions, undoubtedly enhances antigen presentation to the lamina propria and facilitates immune stimulation. The net result is increased production of inflammatory cytokines such as IL-1, IL-6, TNF-α and, most notably, IL-8 [27,28].

Chronic active gastritis is associated with an increased CD4/CD8 T-cell ratio within the gastric mucosa, due
largely to the accumulation of CD4+ T-helper lymphocytes in the lamina propia. *H. pylori* infection results in a Th1-dominant host immune response in the gastric mucosa, characterized by the induction of IFN-γ (interferon-γ) and IFN-γ-related genes. A Th1-dominant immune response is associated with elevated levels of the pro-inflammatory cytokines IL-12, IL-18 and TNF-α[11]. The severity of gastritis associated with *H. pylori* infection was correlated with mucosal expression of the TNF-α subunit CD68 and IFN-γ[29]. A more robust mucosal Th1 response has also been associated with progression to atrophic gastritis and gastric cancer, as supported by animal models[30].

The host genetic background contributes to the immune and inflammatory response to *H. pylori* infection. The *IL-1B* gene encodes the expression of IL-1β, a potent pro-inflammatory cytokine and powerful inhibitor of gastric acid secretion that plays a major role in initiating and amplifying the inflammatory response to *H. pylori* infection[31]. A polymorphic allele with T instead of C at position -511 of the regulatory region of the *IL-1B* gene (*IL-1B -511T*) is associated with increased IL-1β production[32]. *IL-1RN* encodes the IL-1-receptor antagonist, an anti-inflammatory cytokine that competitively binds to IL-1 receptors and thereby modulates the potentially damaging effects of IL-1[33]. The *IL-1RN* gene has a penta-allelic 86 bp variable number tandem repeat in intron 2, of which allele 2 (*IL-1RN*^T^) is associated with a wide range of chronic inflammatory and autoimmune conditions and enhanced IL-1β secretion. Hwang et al.[34] have shown that, in *H. pylori*-infected Japanese subjects, individuals who carried an *IL-1B* gene polymorphism (*IL-1B -511T*) or those carrying the *IL-1RN*^T^ allele had higher mucosal IL-1β levels than non-carriers. These studies demonstrate that host genetic polymorphisms in inflammatory response genes can influence the nature and extent of *H. pylori*-mediated gastritis and thereby disease expression.

**Humoral response**

Individuals colonized with *H. pylori* elicit a strong specific systemic and local antibody response to the infection. Tosi and Czinn[35] reported that binding of IgG to *H. pylori* promoted phagocytosis and killing in vitro by polymorphonuclear leukocytes. *H. pylori* strains are susceptible to complement and activate it either via the classical pathway, even in the absence of specific antibodies, or by the alternative pathway[36,37]. Despite this vigorous immune response, *H. pylori* is not eradicated unless an infected individual is treated with a combination of antibiotics, and lifelong chronic infection usually develops. These observations suggest that gastric mucus may be a protective niche in which *H. pylori* exist and are relatively inaccessible to specific antibodies or their effector functions. The ineffective humoral response generated towards *H. pylori* and its components may actually contribute to pathogenesis. Some of the monoclonal antibodies directed against *H. pylori* cross-react with gastric epithelium of both mice and humans and delivery of these antibodies alone to mice can induce gastritis[2].

Clyne et al.[38] have shown that human serum from both infected and non-infected subjects exerted a bactericidal effect on *H. pylori*. Furthermore heat inactivation abolished the killing effect of the serum samples on the organism, strongly suggesting that it was complement mediated. Later it was reported that bovine normal serum and serum from immunized cows is highly bactericidal for *H. pylori*. This bactericidal effect is destroyed by heating to 56 °C for 30 min and restored by the addition of fetal calf serum as a source of complement, indicating that the bactericidal effect is probably dependent on an antibody–complement system. However, the bactericidal activity did not correlate with titres of specific antibody or with IgG concentrations[39]. In the study by Clyne et al. [38], serum samples from infected subjects killed the organism more effectively than serum from non-infected individuals, indicating that some of this effect is mediated by the classical pathway.

Sampling of gastric secretions from *H. pylori*-infected individuals also reveals an active mucosal antibody response, primarily of the IgA isotype. This response is consistent with the predominance of sIgA (secretory IgA) in the gastric secretions of healthy individuals. sIgA anti-(*H. pylori*) antibodies are also found in saliva and breast milk[11].

Thomas et al.[40] have reported that children in Gambia who were breastfed by mothers that had high titres of specific anti-(*H. pylori*) sIgA in their milk were protected from infection for a longer period than children whose mothers had lower anti-(*H. pylori*) antibody titres. It was postulated that specific antibodies in human milk passed from mother to child during breast feeding are protective against infection by *H. pylori*; however, most children were infected by 12 months of age. Other studies have questioned the role of breast feeding as protective factor in *H. pylori* acquisition. The relationship between infection and childhood home environment has been evaluated in German[41], Japanese[42] and Italian[43] populations. No association was seen between *H. pylori* seropositivity and a history of breast feeding in any of the three studies.

Studies have shown that sIgA can interfere with the ability of some enteric pathogens to establish infection[44,45]. Others have shown that sIgA can inhibit bacterial adherence[46]. However, Clyne et al.[38] have shown that the systemic antibody response and the sIgA response against *H. pylori* do not inhibit the organism from adhering to gastric cells in vitro. This may explain why chronic infection develops in infected subjects despite a vigorous immune response.
IMMUNOMODULATION BY H. PYLORI

To maintain prolonged colonization of the human gastric mucosa, H. pylori must avoid both innate and adaptive immune responses.

Following infection with H. pylori, DCs phagocytose bacterial proteins and express peptides on their surface, together with MHC and co-stimulatory molecules. This presentation of antigens effectively leads to the activation of CD4+ T-cells that react towards these antigens and trigger the immune response. Naive CD4 T-cells can differentiate upon activation into either Th1 or Th2 cells, which differ in the type of cytokines that they produce and therefore in their function. The factors that determine whether a proliferating CD4 T-cell in vivo will differentiate into a Th1 or a Th2 cell are not fully understood. The cytokines elicited by infectious agents (principally IFN-γ, IL-2 and IL-4), the co-stimulators used to drive the response and the nature of the peptide–MHC ligand all have an effect [47].

The consequences of inducing Th1 versus Th2 cells are profound: the selective production of Th1 cells leads to cell-mediated immunity and the production of opsonizing antibody classes (predominantly IgG), whereas the production of predominantly Th2 cells provides humoral immunity, especially IgM, IgA and IgE.

Most intracellular bacteria induce Th1 responses, whereas extracellular pathogens stimulate Th2-type responses. Based on the fact that H. pylori is non-invasive and that infection is accompanied by an exuberant humoral response, one might predict that a Th2 response would be predominant within H. pylori-colonized gastric mucosa. Paradoxically, the majority of H. pylori antigen-specific T-cell clones isolated from infected gastric mucosa produce higher levels of IFN-γ than IL-4, which is reflective of a Th1-type response [48]. H. pylori also stimulates production of IL-12 in vitro, a cytokine that promotes Th1 differentiation. These findings raise the hypothesis that an aberrant host response (Th1) to an organism predicted to induce secretory immune responses (Th2) may influence and perpetuate gastric inflammation. Animal models of H. pylori-induced gastritis have supported these conclusions [49]. Furthermore, a bacterial factor contributing to the initiation of Th1 polarization of H. pylori-specific immune response was recently characterized. Deml et al. [50] identified HcpA (Helicobacter cysteine-rich protein A) as a novel pro-inflammatory and Th1-promoting protein. Using splenic cells of H. pylori-negative naive mice, the authors found that HcpA induces a substantial secretion of pro-inflammatory (IL-6 and TNF-α) and Th1-promoting cytokines (IL-12 and IFN-γ), but no significant release of IL-2 and the Th2-promoting cytokines IL-4 and IL-5.

A major mechanism for self/non-self discrimination by the immune system and establishment of self-tolerance is the clonal deletion of self-reactive T- and B-cells exposed to self-antigens during development in the thymus [51]. The deletion mechanism is not complete, however, and potentially hazardous self-reactive lymphocytes are present in the periphery of normal individuals. It has become increasingly evident that active suppression of self-reactive T-cells by regulatory T-cells takes place in the periphery of normal individuals avoiding the onset of harmful autoimmunity. Three phenotypically distinct subsets of suppressor-regulatory T-cell have been described based on one or more surface-marker antigens and/or cytokine-production profiles: the natural CD4+CD25+ regulatory T-cells (Treg) [52], the IL-10-secreting Tr1 cells [53] and the TGF-β (transforming growth factor-β)-secreting Th3 cells [54], which functionally both in vitro and in vivo have been shown to suppress the proliferation and cytokine secretion of effector T-cells.

The recognition of an important role for regulatory T-cells in the suppression of pathogen-induced inflammatory responses has just started to emerge. Recent evidence suggests that the activation of regulatory T-cells, including both Treg and Tr1 cells, might result in decreased pathological responses and prolonged persistence of infection as a mechanism for the maintenance of pathogen-specific immunological memory [55].

Treg seem to play a role in modulating inflammation in H. pylori infection. A recent study [56] has demonstrated that infection of athymic nu/nu mice with H. pylori resulted in considerably lower colonization in mice reconstituted previously with lymph node cells depleted of Treg compared with those reconstituted with control cells. In another study, Lundgren et al. [57] observed that memory T-cell responses were increased upon specific antigen stimulation of peripheral blood lymphocytes taken from H. pylori-infected subjects when the cell population was depleted of Treg. These studies indicate that Treg may reduce immunopathology in H. pylori gastritis, possibly by reducing activation of IFN-γ-producing CD4+ T-cells, but at the expense of a higher H. pylori bacterial load.

EVASION OF IMMUNE RESPONSE BY H. PYLORI (Figure 1)

Evasion of innate response

NO (nitric oxide) is a key component of the innate immune system and an effective antimicrobial agent [58]. Gobert et al. [59] have shown that H. pylori prevents NO production by host cells by producing the enzyme arginase. This enzyme is encoded by the gene rocF, and competes with NOS2 (NO synthase 2) for the substrate L-arginine and converts it into urea and L-ornithine, rather than NO. Mutation of rocF results in efficient killing of the bacteria in an NO-dependent manner, whereas wild-type bacteria survive under these conditions.
Figure 1  

\[ H. \text{pylori} \] pathogenesis and the inflammatory response

\[ H. \text{pylori} \] resides in the gastric lumen and colonizes the gastric epithelium using urease. Binding of \[ H. \text{pylori} \] to epithelial cells and injection of CagA results in the production of IL-8 and other chemokines, and activation of the innate and adaptive immune systems. To evade the immune response, \[ H. \text{pylori} \] has evolved mechanisms to reduce recognition by immune sensors, down-regulate activation of immune cells and escape immune effectors. PMN, polymorphonuclear cells.

Furthermore, the \textit{rocF} mutant is mildly attenuated in its ability to colonize mice.

It has been shown that, during \[ H. \text{pylori} \] infection, bacteria can survive intracellularly within macrophages by interfering with lysosomal proteins, similar to \textit{Mycobacterium tuberculosis} [60]. Therefore, although there is an innate response to the bacteria, it is not effective enough to eliminate the infection. In one study, Allen et al. [61] have shown a delayed uptake of bacteria into macrophages followed by the formation of megasomes as a result of phagosome fusion. These megasomes protect intracellular bacteria from efficient killing. Furthermore, using human blood monocytes and polymorphonuclear cells, Ramarao et al. [62] have shown that \[ H. \text{pylori} \] can actively block its own uptake, as well as the uptake of co-cultured bacteria of other species and latex beads. Both of these phenotypes depended on the presence of Cag-PAI.

Bacterial LPSs are classic mediators of inflammation, because of their activation of phagocytic cells, endothelial and epithelial cells and lymphocytes [63]. However, despite a general conservation of LPS structure, large differences in their pro-inflammatory activity have been noted. When compared with LPS from Enterobacteriaceae, \[ H. \text{pylori} \] LPS is 1000-fold less active and only weakly activates macrophages [64]. Therefore it has been suggested that there is selective pressure in \[ H. \text{pylori} \] cells to minimize pro-inflammatory activities to permit long-term colonization, since enhanced inflammation, leading to atrophic gastritis, would lead to a loss of niche.

Finally, it has been recently demonstrated [65] that members of the \alpha and \epsilon Proteobacteria, including \[ H. \text{pylori} \], possess flagellin molecules that cannot be recognized by TLR5. Their unique flagellin sequences contain amino acid differences in the TLR5 recognition site that permit TLR5 evasion, as well as compensatory mutations that preserve bacterial motility. These results suggest that TLR5 evasion is critical for the survival of \[ H. \text{pylori} \] at mucosal sites.

**Evasion of adaptive response**

\[ H. \text{pylori} \] has evolved to subvert not only the innate, but also the adaptive immune response. It has been shown that \[ H. \text{pylori} \] specifically can block antigen-dependent proliferation of T-cells. This effect is mediated by the virulence factor VacA, which acts as an immunomodulator by interfering with the IL-2 signalling pathway in T-cells by blocking Ca\(^{2+}\) mobilization and the activity of the Ca\(^{2+}\)/calmodulin-dependent phosphatase calcineurin [66]. Another possible function of VacA in subverting the adaptive immune response is its ability to interfere
with antigen presentation mediated by MHC class II [67]. A recent study [68] strongly supports the possibility that VacA is immunosuppressive, but the mechanism described involves a direct action on T-cells rather than APCs. The authors [68] show that the toxin inhibits the activation and proliferation of T-cells.

Several findings indicate that a strong inflammatory reaction is necessary for the elimination of H. pylori and, at least in animal models, it seems to be actively repressed by the bacterium: an increased inflammatory reaction, as seen in IL-10 knockout mice, is associated with clearance of H. pylori from the stomach within 8 days of the infection [69]. Similarly, increased inflammation due to deletion of the gene encoding PHOX (NADPH oxidase) results in a marked reduction in bacterial numbers [70].

Genomic DNA recombination has been shown to be critical for mediating persistence of H. pylori through the induction of ineffective immune responses. Robinson et al. [71] found that the H. pylori wild-type strain and the ruvC mutant (which encodes a Holliday junction resolvase) elicited oppositely polarized Th2 cell responses that correlated with persistence and clearance respectively. Temporary colonization by the ruvC mutant conferred significant protection against subsequent challenge with the wild-type strain.

**CLINICAL OUTCOMES**

Everyone who carries H. pylori in their stomach develops a cellular infiltrate in their gastric mucosa, termed chronic gastritis (Figure 2). In most patients (80%), H. pylori does not cause clinical symptoms and the infection can persist for a lifetime without further problems. A proportion (10–20%) of infected patients will develop gastric hyperacidity and peptic ulcers, but can be cured by antibiotic treatment. However a small percentage (0.1–4%) of infected patients will develop distal gastric adenocarcinoma, depending on the circumstances of the infection and the individual immune response towards the bacterium.

Although the factors determining this variable outcome are not well understood, the development of a sustained gastric inflammatory and immune response to infection appears to be pivotal for the development of disease [72]. Mucosal T-cells in infected individuals are polarized towards the production of IFN-γ, rather than IL-4 or IL-5, indicating a strong bias towards a Th1-type response [48].

Bacterial determinants of virulence are considered critical for initiating close interactions with host epithelial cells and inducing mucosal inflammation. H. pylori strains containing the cag-PAI are associated with more severe antral inflammation, higher mucosal levels of IL-1β and IL-8 [73], peptic ulceration [74] and increased acid secretion [75].

Other virulence-independent factors, such as the duration and density of infection, may also influence the outcome, but have been studied less well. Surveys of the early phases of infection (in children) are few, but indicate that a pro-inflammatory response and Th1-type cytokines were
detected in response to infection [76,77]. In contrast with adults, in whom neutrophilic infiltrates predominate, children develop a predominantly mononuclear infiltrate and have a higher degree of lymphoid follicular hyperplasia. The mechanisms underlying the differences in histopathology and disease pattern between children and adults and the early and late stages of infection are still not well understood.

Recent studies have begun to shed light on specific host genetic determinants of risk for H. pylori-associated disease outcomes. Polymorphisms that increase the IL-1β response to H. pylori are associated with an increased risk of developing hypochlorhydria, gastric atrophy and adenocarcinoma [78,79]. In a large population-based case-control study of gastrointestinal carriers, El Omar et al. [80] recently demonstrated that pro-inflammatory genotypes of TNF-α and IL-10 were each associated with more than doubling the risk of noncardia gastric cancer and that carriage of multiple pro-inflammatory polymorphisms conferred even greater risks.

When the influence of CagA and VacA status on histological changes was analysed in subjects stratified according to IL-1B and IL-RN polymorphisms, it appeared that more severe gastric abnormalities correlated both with high-risk polymorphisms (IL-1B – 511T and IL-RN+2 alleles) and virulence factors (cagA / vacAs1+). In vacAs1/IL-1B – 511T patients and cagA-positive/ IL1RN+2/-2, the odds ratios for gastric carcinoma were 87 [95% CI (confidence intervals), 11–679] and 23 respectively [95% CI, 7.0–72] [81].

CONCLUSIONS

H. pylori continues to be one of the most common bacterial infections in humans, colonizing the stomach and persisting for the host’s lifetime. Although the human host mounts a vigorous innate and adaptive immune response against the bacterium, H. pylori escapes and evades host responses by a variety of mechanisms, leading to persistent colonization and chronic active inflammation. An intriguing characteristic of H. pylori-induced gastritis is its capacity to persist for decades without causing serious damage in most cases. In its long association with humans, H. pylori has established a fine balance between establishing a comfortable niche and avoiding the immune consequences of its colonization. Clinical complications of H. pylori colonization, such as peptic ulcer disease and gastric cancer, are therefore likely to represent imbalances in gastric homoeostasis that are disadvantageous for both microbe and host, particularly if death of the host ensues. Considerable efforts have focused on delineating the precise mechanisms by which H. pylori colonization leads to gastric inflammation. It is likely that the polarized Th1 responses and the inflammatory cytokines induced by H. pylori gene products play major roles in the gastric epithelial inflammation associated with H. pylori disease. Genetic or environmentally influenced variability in the propensity to mount these types of inflammatory responses may, at least in part, help to explain the different outcomes of H. pylori-induced disease in different individuals.

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REFERENCES


© 2006 The Biochemical Society
Interleukin-1 polymorphisms are associated with increased risk of gastric cancer. Nature (London) 462, 1247–1255


Rugge, R. F., Fan, X., Crowe, S. E. et al. (1998) Lymphocytes in the human gastric mucosa during Helicobacter pylori infection have a T helper cell 1 phenotype. Gastroenterology 114, 482–492


69 Luzza, F., Parello, T., Sebeka, L. et al. (2001) Expression of proinflammatory and Th1 but not Th2 cytokines is enhanced in gastric mucosa of *Helicobacter pylori* infected children. Dig. Liver Dis. 33, 14–20


