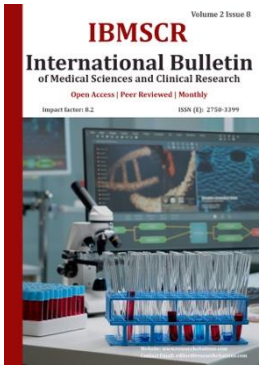

IMMUNE RESPONSE TO HELICOBACTER PYLORI ANTIGENS AND ITS IMPLICATIONS IN GASTRIC PATHOLOGY

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Abstract

Helicobacter pylori (*H. pylori*) is a Gram-negative bacterium with a marked affinity for gastric tissue and is globally recognized as a major cause of gastrointestinal disease. Chronic infection with *H. pylori* is implicated in a wide spectrum of disorders, including peptic ulcer disease, gastric adenocarcinoma, mucosa-associated lymphoid tissue (MALT) lymphoma, and several extra-gastric complications. The bacterium expresses multiple virulence factors—such as lipopolysaccharides (LPS), cytotoxin-associated gene A (CagA), vacuolating cytotoxin A (VacA), and a range of adhesins—that provoke a strong host immune response during the early stages of infection.

Notably, the lipid A component of *H. pylori* LPS displays markedly reduced endotoxic activity compared with typical bacterial LPS, a feature that facilitates persistent colonization by enabling immune evasion. Initial host defense involves the recruitment and activation of innate immune cells—neutrophils, monocytes, and macrophages—that phagocytose and destroy the bacteria. These cells, together with gastric epithelial cells, release cytokines and chemokines that attract adaptive immune effectors, including Th1 and Th17 lymphocytes, which are crucial for bacterial clearance.

However, in many individuals, a disruption of this immunological balance results in a shift toward immune tolerance, characterized by the expansion of regulatory T (Treg) cells. These Treg cells produce interleukin-10 (IL-10), which suppresses Th1- and Th17-mediated cytokine responses, thereby promoting bacterial persistence and chronic gastric inflammation. In parallel, the humoral immune response contributes to mucosal damage: B-cell activation leads to the generation of autoreactive antibodies, including anti-Lex IgG, which can target host gastric tissues through molecular mimicry mechanisms.

This review discusses the molecular and immunological interactions between *H. pylori* and the host, highlighting how its antigenic structures modulate innate and adaptive immune responses and contribute to the pathogenesis of *H. pylori*-induced gastric disease.

Keywords: *Helicobacter pylori*; gastric pathology; host immunity; immune evasion; molecular mimicry; immunoregulation

Introduction

Helicobacter pylori (*H. pylori*) is a microaerophilic, spiral-shaped, Gram-negative bacterium that colonizes the human gastric mucosa and infects nearly **half of the global population**. Its persistence within the stomach is strongly associated with a variety of gastrointestinal disorders—including **chronic gastritis, peptic and duodenal ulcers, mucosa-associated lymphoid tissue (MALT) lymphoma, and gastric carcinoma**—as well as several **extra-gastric pathologies**. The bacterium's long-term survival in such a hostile

acidic environment is largely attributed to its sophisticated **immune evasion strategies**, which enable it to evade host defenses and establish chronic infection.

Several **pathogenic mechanisms** contribute to *H. pylori*'s persistence and virulence. One of the bacterium's key enzymes, **urease**, neutralizes gastric acid by hydrolyzing urea into ammonia and carbon dioxide, thereby creating a microenvironment conducive to its survival. In addition, *H. pylori*'s **flagellar motility** allows it to penetrate the mucus layer and reach the epithelial surface, where it adheres firmly to gastric epithelial cells via specific **adhesin–receptor interactions**, thus establishing colonization.

Upon adhesion, *H. pylori* deploys a series of **virulence factors** that profoundly alter host cellular processes. Among these, **cytotoxin-associated gene A (CagA)** and **vacuolating cytotoxin A (VacA)** play central roles in the pathogenesis of gastric disease. CagA disrupts intracellular signaling cascades—including the **mitogen-activated protein kinase (MAPK)** and **phosphatidylinositol 3-kinase (PI3K)** pathways—thereby inducing morphological changes in epithelial cells, suppressing immune defenses, and promoting **carcinogenic transformation**. Conversely, VacA forms **anion-selective pores** in host cell membranes, leading to mitochondrial dysfunction, autophagy, apoptosis, and suppression of **effector T-cell activity**. Together, CagA and VacA maintain a chronic inflammatory milieu within the gastric mucosa while simultaneously facilitating *H. pylori*'s **immune escape**.

Another major factor in *H. pylori*'s persistence is the unique composition of its **lipopolysaccharide (LPS)**. Unlike LPS from other Gram-negative bacteria such as *Escherichia coli* or *Salmonella*, *H. pylori* LPS possesses markedly **reduced endotoxicity**. This is primarily due to structural modifications in its **lipid A moiety**, which contains tetra-acyl chains (16–18 carbons long) that diminish recognition by **Toll-like receptors (TLRs)** on epithelial cells, neutrophils, monocytes, and macrophages. Consequently, the host's **innate immune activation** is blunted, allowing the bacterium to persist without eliciting a full protective inflammatory response.

The **gastric immune response** to *H. pylori* infection is biphasic. In the **early phase**, bacterial antigens stimulate an intense **innate immune reaction**, characterized by the recruitment and activation of **neutrophils, monocytes, and macrophages**, which phagocytose bacteria and secrete **pro-inflammatory cytokines and chemokines**. A key mediator, **interleukin-8 (IL-8)**, promotes the recruitment of additional immune cells—including T and B lymphocytes—to the infection site, sustaining local inflammation. However, under chronic antigenic stimulation, immune homeostasis can become disrupted, resulting in the expansion of **regulatory T (Treg) cells**. These cells secrete **interleukin-10 (IL-10)** and **transforming growth factor-beta (TGF-β)**, suppressing Th1- and Th17-mediated immunity and promoting **immune tolerance**, which facilitates persistent bacterial colonization.

Furthermore, *H. pylori* infection downregulates the expression of **epidermal growth factor (EGF)** and **TGF-β**, both of which are essential for gastric mucosal repair. The failure of epithelial regeneration, combined with prolonged inflammation, enhances the risk of **neoplastic transformation** and **gastric carcinogenesis**.

Major Antigenic Components of *Helicobacter pylori*

Like other Gram-negative bacteria, *Helicobacter pylori* (*H. pylori*) possesses a **lipopolysaccharide (LPS)** structure composed of three principal regions: the **O-**

polysaccharide chain, the **core oligosaccharide**, and the **lipid A** moiety that anchors the molecule to the bacterial outer membrane. However, *H. pylori* LPS differs substantially from that of other enteric bacteria, displaying **markedly reduced endotoxic potency**. The lipid A component of *H. pylori* contains **long-chain fatty acids** (typically 16–18 carbons) and is predominantly **tetra-acylated**, in contrast to the hexa-acylated lipid A of *Escherichia coli* and *Salmonella* species. This reduced acylation is mediated by an **outer membrane deacylase enzyme (Jhp0634)**, which selectively removes the acyl chain at the 3′ position, resulting in a lipid A structure with attenuated immunostimulatory activity.

In comparison, the lipid A of *Salmonella minnesota* or *E. coli* retains a higher degree of acylation and specific fatty acid composition essential for their potent **biological and toxic effects**. Because of these structural differences, *H. pylori* lipid A elicits a much weaker activation of host immune pathways. It induces minimal release of **cytokines, nitric oxide (NO), and prostaglandin E_2,** and shows a diminished capacity to stimulate **natural killer (NK) cells**, **selectin expression**, and **T regulatory (Treg) cell downregulation**. Consequently, *H. pylori* lipid A contributes to the bacterium's **ability to evade host defenses**, thereby facilitating persistent gastric colonization and chronic infection.

The **O-polysaccharide antigen** of *H. pylori* is another important immunogenic structure. Although highly conserved, it undergoes **fucosylation**, leading to molecular structures that **mimic human Lewis blood group antigens**, including **Le^x, Le^y, Le^a, Le^b, Le^c, sialyl-Le^x,** and the **H-1 antigen**. This **molecular mimicry** allows *H. pylori* to camouflage itself from immune detection and may also trigger **autoimmune reactions**. Inactivation of the *H. pylori* Le^x and Le^y determinants has been shown to impair bacterial colonization in animal models, supporting their role in adhesion and persistence. The resemblance between *H. pylori* O-antigen structures and host glycans can provoke the production of **autoreactive anti-Le^x and anti-Le^y antibodies**, which contribute to **gastric mucosal injury**. Moreover, the *H. pylori* Le^x epitope specifically binds to the **galectin-3 receptor** on gastric epithelial cells, reinforcing bacterial attachment and immune modulation through host–pathogen glycan interactions.

Among *H. pylori*'s protein antigens, two virulence factors—**Cytotoxin-associated gene A (CagA)** and **Vacuolating cytotoxin A (VacA)**—play pivotal roles in disease pathogenesis. Approximately 70% of *H. pylori* strains express **CagA**, which is delivered into host epithelial cells via a **type IV secretion system (T4SS)**. This system forms a **pilus-like structure** that binds to host **β1 integrin receptors**, enabling the translocation of CagA into the cytoplasm. Once inside, CagA undergoes **tyrosine phosphorylation** and activates the **MAPK** and **PI3K** signaling pathways, resulting in cytoskeletal rearrangements, altered cell morphology, immune suppression, and, in some cases, **carcinogenic transformation**.

VacA, a secreted toxin of approximately 88 kDa, comprises two major domains: an **N-terminal p33 domain**, responsible for **pore formation**, and a **C-terminal p55 domain**, which mediates **receptor binding**. These domains are linked by a protease-sensitive flexible loop. The vacuolating activity of VacA disrupts **intercellular junction proteins** such as **E-cadherin, occludin, and claudin-8**, leading to the breakdown of **gastric epithelial barrier integrity**, increased cell permeability, and the induction of **mitochondrial stress, apoptosis, and autophagy**.

In addition to these factors, *H. pylori* releases **outer membrane vesicles (OMVs)**—spherical particles ranging from 20 to 30 nm in diameter—that act as vehicles for long-distance

delivery of virulence molecules. These vesicles contain **LPS, phospholipids, CagA, VacA**, and multiple **adhesins** (such as SabA, BabA, AlpA, AlpB, OipA, and Hop2), along with enzymatic components like **urease, catalase,** and **serine protease**. OMVs contribute to biofilm formation on the gastric mucosal surface, providing the bacteria with enhanced protection against **immune attacks** and **antimicrobial agents**.

Once internalized by gastric epithelial cells, *H. pylori* OMVs stimulate the production of **interleukin-8 (IL-8)**, which recruits **T cells, B cells, NK cells, and monocytes** to the infection site. These infiltrating immune cells penetrate the **gastric lamina propria**, where they sustain chronic inflammation and, paradoxically, exert **immunosuppressive effects**, further weakening the host's protective response.

The major components of H.p. organisms are summarized in Figure 1.

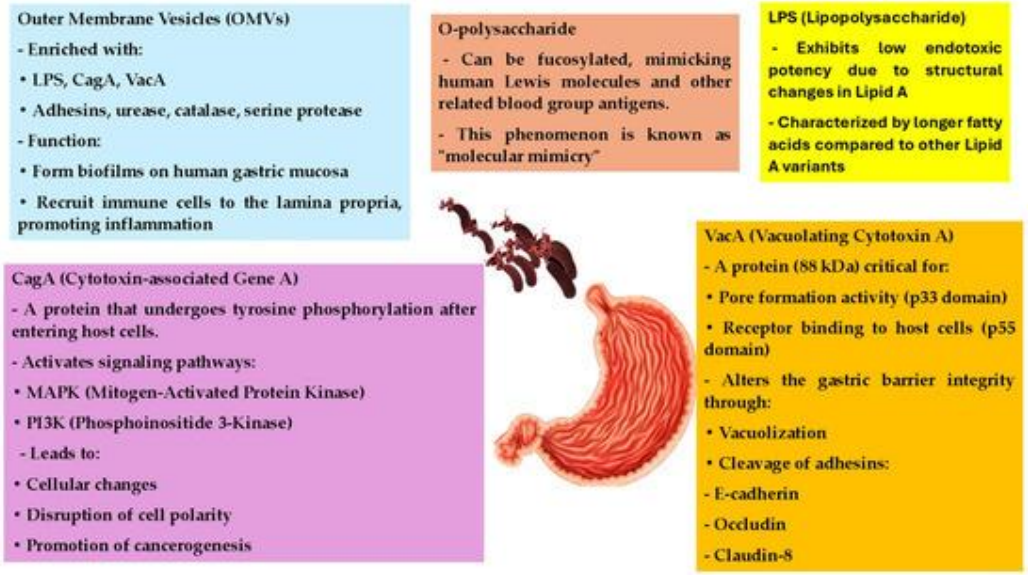

Figure 1. Antigenic components of Helicobacter pylori (H.p.).

Pathogenesis of *Helicobacter pylori* Infection

The initial step in *Helicobacter pylori* (*H. pylori*) infection involves **bacterial adhesion to the gastric mucosa**, which is guided by **chemotactic responses** to host-derived signals. The bacterium's **TlpB receptor family** detects chemical gradients formed by **urea, lactic acid, reactive oxygen species (ROS), and components of gastric juice**, directing bacterial movement toward the epithelial surface. *H. pylori*'s **flagellar motility** enables it to navigate through the viscous gastric mucus layer and establish close contact with epithelial cells, ultimately leading to **successful colonization** of the gastric mucosa.

Once attached, *H. pylori* often forms **biofilms** within an **extracellular matrix**, which provide mechanical and chemical protection from host immune defenses and antibiotic agents. This biofilm mode of growth enhances bacterial persistence and contributes to the chronicity of infection. Following adhesion, the bacterium deploys an array of **virulence factors** to manipulate host cellular pathways and weaken protective immune responses.

Among these factors, **cytotoxin-associated gene A (CagA)** plays a pivotal role. Upon **tyrosine phosphorylation**, CagA aberrantly activates intracellular signaling cascades such as the **mitogen-activated protein kinase (MAPK)** and **phosphatidylinositol 3-kinase (PI3K)** pathways. These events trigger **morphological alterations in epithelial cells**, disrupt **cell**

polarity, stimulate the **release of pro-inflammatory cytokines and chemokines**, and initiate **oncogenic processes** that contribute to gastric carcinogenesis.

The **vacuolating cytotoxin A (VacA)** protein exerts additional pathogenic effects. By forming **pores and ion-permeable channels** in gastric epithelial membranes, VacA increases cellular permeability and induces **mitochondrial stress**. Depending on the context, VacA can elicit either **pro-apoptotic or anti-apoptotic effects**, promote **autophagy**, and amplify **inflammatory responses** through **cytokine release**, **inflammasome activation**, and **T-cell modulation**. Importantly, CagA and VacA act **synergistically** to disturb the **nuclear factor of activated T cells (NFAT) signaling pathway**, enhancing **p21 gene expression**, disrupting **cell-cycle regulation and differentiation**, and thereby fostering **neoplastic transformation** of gastric cells.

Another critical virulence determinant is **urease**, an enzyme abundantly produced by *H. pylori*. Urease catalyzes the hydrolysis of **urea into ammonia and carbon dioxide**, generating a **localized neutral microenvironment** that shields the bacterium from the stomach's highly acidic conditions. This mechanism is essential for bacterial survival and persistent colonization.

Within the gastric mucosa, *H. pylori* interacts extensively with the **host immune surveillance system** by engaging **pattern recognition receptors (PRRs)**—notably **Toll-like receptors (TLRs)** and **nucleotide-binding oligomerization domain-like receptors (NLRs)**. TLRs, expressed on **antigen-presenting cells** such as macrophages and dendritic cells, recognize conserved microbial components and link **innate and adaptive immune responses**. Meanwhile, the activation of **NLRs** promotes **inflammasome formation**, leading to **caspase activation** and the release of **pro-inflammatory cytokines**, including **interleukin-1β (IL-1β)** and **interleukin-8 (IL-8)**.

H. pylori **LPS** binds to TLRs on **epithelial cells, monocytes, and macrophages**, activating **NF-κB** signaling and inducing the secretion of **pro-inflammatory mediators** such as **IL-1β, tumor necrosis factor-alpha (TNF-α),** and **IL-8**. In addition, **TLR7, TLR8, and TLR9** recognize bacterial **DNA and RNA**, while **TLR2 and TLR5** detect **cell wall components and flagellin**, respectively. Certain **host TLR gene polymorphisms**, particularly in **TLR1** and **TLR10**, are linked to a heightened risk of **gastric cancer** in infected individuals.

The engagement of PRRs triggers downstream signaling cascades through adaptor proteins such as **MyD88** and **TRIF**, leading to activation of **NF-κB**, **MAPK**, and **interferon regulatory factors (IRFs)**. This culminates in the enhanced production of **pro-inflammatory cytokines** (e.g., IL-1β and TNF-α) and the **recruitment of neutrophils and monocytes** to the infection site, which collectively form the first line of host defense against *H. Pylori.*

The pathogenetic events triggered by H.p. are indicated in Table 1.

Table 1. Pathogenesis of *Helicobacter pylori* (*H.p.*) infection.

H.p. adheres to gastric epithelial cells through the TlpB receptor activated by urea, lactic acid, reactive oxygen species, and gastric juice, with motility depending on the flagella.
CagA and VacA induce the release of cytokines and chemokines, inflammasome activation, and T cell proliferation.
Urease allows for the survival of H.p. in the low-pH acidic gastric milieu.

H.p. LPS binds to TRLs present on host cells, with TLR4 inducing the release of pro-inflammatory cytokines, e.g., interleukin (IL)-1 beta, IL-8, and tumor necrosis factor (TNF)-alpha, with TLR7, TLR8, and TLR9 recognizing H.p. DNA, RNA, and TLR2 and TLR5 recognizing cell wall components and flagellin.

During H.p. infection, MyD88 and TRIF activate NF-kB, MAPKs, and interferon regulatory factors through the release of IL-1 beta and TNF-alpha and the recruitment of innate immune cells.

H. pylori–Mediated Modulation of the Innate Immune Response

The host's immune reaction to *Helicobacter pylori* (*H. pylori*) infection is initiated by the recognition of **pathogen-associated molecular patterns (PAMPs)** through **pattern recognition receptors (PRRs)**, including **Toll-like receptors (TLRs)**, **nucleotide-binding oligomerization domain-like receptors (NLRs)**, **C-type lectin receptors (CLRs)**, and **retinoic acid–inducible gene I (RIG-I)-like receptors (RLRs)**, which are expressed on **innate immune cells** and **gastric epithelial cells**.

Among these, **TLR4** is preferentially engaged by *H. pylori* **lipid A**, although the resulting inflammatory response is relatively weak. Experimental studies have demonstrated that **dephosphorylation of lipid A**—through removal of phosphate groups at the 1′ and 4′ positions—diminishes the molecule's endotoxic potency, thereby mimicking the naturally attenuated activity of *H. pylori* lipid A. Moreover, **mutations in TLR4 or its co-receptor MD-2** further reduce receptor activation, highlighting *H. pylori*'s ability to **evade immune detection** at the receptor level.

In contrast, **TLR2** becomes activated upon interaction with *H. pylori* **neutrophil-activating protein (NAP)**, leading to the release of **interleukin-8 (IL-8)**, a chemokine that attracts neutrophils and macrophages to the site of infection. *H. pylori*'s **flagellin** is also atypical: due to specific amino acid substitutions (R89T, L93K, and E114D), it exhibits **poor antigenicity** and fails to effectively activate **TLR5**, further contributing to the bacterium's immune evasion strategy.

During infection, the **RIG-I-like receptor (RLR)** and **STING** signaling pathways are modulated by *H. pylori*, leading to **Th17-driven inflammation** characterized by elevated expression of the regulatory protein **Trim30a**. Concurrently, activation of the **NLRP3 inflammasome** via TLR2 recognition induces the production of **interleukin-1β (IL-1β)** and promotes **T regulatory (Treg) cell differentiation**, ultimately dampening protective host immunity and facilitating bacterial persistence.

H. pylori infection also significantly alters **macrophage function**. Binding of *H. pylori* **LPS** to **CD14** and **TLR4** stimulates **NF-κB** activation and the release of **pro-inflammatory cytokines** such as IL-1β, IL-6, and **tumor necrosis factor-alpha (TNF-α)**—a process that initially benefits host defense. However, *H. pylori* simultaneously inhibits macrophage **phagocytosis** and **endocytosis** by interfering with the **PI3K/Akt** and **JAK/STAT** signaling pathways, thereby impairing bacterial clearance. Consequently, *H. pylori* can elicit **dual immune outcomes**, either activating protective inflammation or promoting immune suppression, depending on the balance of local immune homeostasis.

Furthermore, **CagA** disrupts macrophage activity by binding to **E-cadherin** and **β1 integrin**, or by preventing **phagosome–lysosome fusion**, thus blocking phagolysosomal acidification. Similarly, outer membrane proteins (OMPs) such as **BabA** and **SabA** interfere with macrophage cytoskeletal organization, further hindering **phagolysosome formation**. The combined binding of **LPS, CagA, and VacA** to macrophages elevates **intracellular calcium levels**, leading to **mitochondrial dysfunction**, impaired phagocytosis, and **apoptosis**.

CagA also modulates macrophage polarization by inducing **heme oxygenase-1 (HO-1, encoded by HMOX1)**, which shifts the macrophage balance from the **pro-inflammatory M1 phenotype** toward the **immunosuppressive M2 phenotype**. M1 macrophages typically eliminate pathogens through **reactive oxygen species (ROS)** production and the recruitment of **Th1** and **natural killer (NK)** cells, while M2 macrophages produce **interleukin-10 (IL-10)** and low levels of **interleukin-12 (IL-12)**, thereby attenuating Th1 activation. HO-1–mediated polarization toward M2 macrophages suppresses effective antibacterial responses and supports *H. pylori* survival.

In the setting of **chronic gastritis**, *H. pylori*–induced **nitric oxide (NO)** production can inhibit the M1-to-M2 transition, whereas the reduction of NO favors reprogramming toward the M2 phenotype. Moreover, the bacterium induces **arginase-2 expression** in macrophages, depleting **L-arginine** and reducing **NO-mediated bactericidal activity**, while simultaneously impairing **Th1/Th17 cell differentiation**. These effects collectively facilitate **bacterial persistence** during chronic infection. *H. pylori* also upregulates **ornithine decarboxylase (ODC)**, promoting a shift toward M1 macrophages, and regulates the M1/M2 balance through **cystathionine γ-lyase (CTH)**. Experimental models using CTH-deficient mice have shown that the absence of this enzyme favors M1 polarization during infection.

Beyond macrophages, *H. pylori* modulates other **innate immune effectors**, including **innate lymphoid cells (ILCs)**. ILCs are divided into three major subsets:

- **ILC1**, which primarily comprises NK cells;
- **ILC2**, which secretes Th2-type cytokines such as IL-5 and IL-13; and
- **ILC3**, which includes **lymphoid tissue inducer (LTi)** cells and both **NCR$^+$** and **NCR$^-$** subsets.

Natural killer (NK) cells, the predominant ILC1 population, are large granular lymphocytes that destroy infected or malignant cells. In *H. pylori*–infected individuals, **CD8$^-$CD16$^-$CD56$^+$ bright NK cells** directly recognize bacterial components and secrete **interferon-gamma (IFN-γ)**, while also responding indirectly through cytokine-mediated activation. However, *H. pylori* **LPS** suppresses NK cell cytotoxicity, resulting in decreased production of **IFN-γ, IL-2, and IL-10** by peripheral blood lymphocytes, thereby compromising antimicrobial defense.

In the gastrointestinal tract, **ILC3s** play a protective role by producing **interleukin-22 (IL-22)** and **interleukin-17 (IL-17)**, which help maintain mucosal integrity and limit systemic inflammation during *H. pylori* infection.

The effects of H.p. infection on the innate immune response are reported in Table 2.

Table 2. *Helicobacter pylori* (*H.p.*)-mediated modulation of innate immune response.

The binding of LPS, CagA, and Vac A to macrophages increases intracellular calcium, hampering the formation of the phagolysosome.
The LPS-mediated activation of NF-kB interferes with the PI3K, Akt, and JAK/Stat signaling pathways, thus inhibiting macrophage phagocytosis.
The *H.p.*-mediated induction of hemeoxygenase 1 inhibits M1 macrophages, shifting the balance toward the suppressive M2 subset of macrophages.
In *H.p.*-mediated chronic gastritis, the inhibition of nitric oxide release polarizes the macrophage response toward the M2 subset.
In *H.p.* infection, the upregulation of ornithine decarboxylase shifts the M1/M2 macrophage balance toward the M1 phenotype.
In cystathionine gamma-lyase knockout mice infected with *H.p.*, there is a shift toward the M1 subset.
H.p. LPS downregulates natural killer cell cytotoxicity, with lower production of interferon-gamma, interleukin (IL)-2, and IL-10.
Innate lymphoid cells 3, upon activation with *H.p.*, generate IL-22 and IL-17, preventing systemic inflammation.

H. pylori–Mediated Modulation of the Adaptive Immune Response

The influence of *Helicobacter pylori* (*H. pylori*) on the **adaptive immune system** has been extensively explored, revealing its capacity to manipulate both **cellular and humoral immunity** to ensure long-term persistence within the host.

Experimental studies in mice have shown that exposure to *H. pylori* components enriched in **lipopolysaccharide (LPS)** and **Cytotoxin-associated gene A (CagA)** proteins triggers a **strong T helper 1 (Th1)** response while concurrently suppressing **Th2 activity**. Specifically, *H. pylori* LPS promotes the secretion of **interferon-gamma (IFN-γ)** and **interleukin-12 (IL-12)**, while downregulating **interleukin-2 (IL-2)**, a cytokine essential for Th2 differentiation. This Th1-dominant immune profile contributes to inflammation but fails to achieve effective bacterial clearance.

Interestingly, *H. pylori* strains expressing **Lewis antigens** can bind to the **DC-SIGN C-type lectin receptor** on gastric T cells, thereby **inhibiting Th1 cell differentiation**—a phenomenon not observed with Lewis-negative strains. This suggests that molecular mimicry through Lewis antigen expression is a crucial strategy for immune evasion.

Another major virulence factor, **Vacuolating cytotoxin A (VacA)**, exerts multiple immunomodulatory effects on T cells. By binding to the **β2-integrin subunit (CD18)**, VacA alters cell morphology and suppresses T-cell activation. It also induces **vacuolization** in T cells through its interaction with **LAF-1**, disrupting cellular integrity and signaling. Conversely, VacA can activate **NF-κB** through the classical pathway in T cells, promoting a **pro-inflammatory response**, which paradoxically contributes to chronic gastritis rather than bacterial clearance.

During *H. pylori* infection, **Th17 cells** play a central role in antimicrobial defense by secreting **interleukin-17 (IL-17)**, which enhances bacterial phagocytosis and destruction through **TLR2** and **TLR4** activation. Th17 cells also release **IL-12** and **IL-2**, facilitating the activation of **Th1 cells** and the production of **IFN-γ** and **tumor necrosis factor-alpha (TNF-α)**. Additionally, **neutrophil extracellular traps (NETs)** have been shown to promote Th17 differentiation through **TLR2-dependent pathways**. Collectively, these cytokine networks form a coordinated defense mechanism involving **IL-2, IL-12, and IL-17**, which initially support host protection against infection.

However, in the chronic phase of infection, this protective equilibrium is disrupted. The **secretion of interleukin-23 (IL-23)** by gastric epithelial cells and the **CagA-mediated suppression of B7-H2 expression** on antigen-presenting cells progressively downregulate **Th17 effector activity**. This shift favors the expansion of **regulatory T cells (Tregs)**, marking a transition from protective to tolerogenic immunity.

VacA plays a decisive role in this transition by acting on **myeloid cells within the gastric lamina propria**, driving the differentiation of **$CD25^+Foxp3^+$ Treg cells**. These Tregs release **interleukin-10 (IL-10)**, a potent anti-inflammatory cytokine that suppresses Th1 and Th17 activity, thereby weakening host defenses and facilitating *H. pylori* persistence. Experimental evidence demonstrates that mice lacking $CD25^+$ T cells show **reduced gastric colonization** by *H. pylori*, whereas those reconstituted with $CD25^+$ lymphocytes exhibit higher bacterial loads. Moreover, spleen cells from $CD25^-$-transplanted mice produce significantly greater amounts of **IFN-γ** upon *H. pylori* stimulation, accompanied by massive infiltration of macrophages and T cells into the gastric mucosa, indicating enhanced bacterial clearance.

In human studies, *H. pylori* exposure has been associated with a marked **increase in peripheral $CD25^+$ Treg cells**, which correlates with the suppression of **T-cell memory responses** and the establishment of **chronic infection**.

Beyond T-cell modulation, *H. pylori* also interferes with **cytokine signaling regulation**. During infection, **suppressor of cytokine signaling (SOCS)** proteins are upregulated, binding to **STAT** molecules at phosphorylated sites on cytokine receptors. This interaction blocks downstream signal transduction, attenuates pro-inflammatory cytokine activity, and contributes to **immune escape** and the **development of chronic gastritis.**

During *Helicobacter pylori* (*H. pylori*) infection, profound alterations occur in **B-cell function and antibody production**, contributing both to protective and pathogenic immune outcomes. Approximately half of *H. pylori*–positive individuals develop **autoreactive antibodies**, which tend to decline following successful bacterial eradication. This autoreactivity is largely attributed to **molecular mimicry**, whereby *H. pylori* antigens share structural similarity with host components. Key antigens implicated in this phenomenon include **heat-shock protein 60**, **Lewis (Le) blood-group antigens**, and the **H^+/K^+-ATPase** of gastric parietal cells.

Among these, **anti-Lewis antibodies**—particularly those directed against **Lex determinants**—are most frequently observed. Anti-Lex **IgM** antibodies appear to exert a **protective effect**, whereas **anti-Lex IgG** antibodies are associated with **gastric mucosal injury** and may contribute to *H. pylori*–related gastropathy. In patients with **duodenal ulcers**, elevated levels of **IgG antibodies targeting smooth forms of** *H. pylori* **lipopolysaccharide (LPS)** have been detected, exceeding those directed against the rough LPS variants.

Additionally, **IgA antibodies** reactive with rough-type LPS have been observed, suggesting that *H. pylori* infection can expose hidden core structures of the bacterial LPS, thereby enhancing mucosal immune recognition.

However, excessive and prolonged **B-cell stimulation** during chronic *H. pylori* infection may have pathological consequences. The continuous activation and expansion of B cells within the **gastric lamina propria** can lead to the formation of **lymphoid aggregates**, which, over time, may evolve into **mucosa-associated lymphoid tissue (MALT) lymphoma**. This demonstrates how chronic antigenic stimulation by *H. pylori* transforms a protective immune mechanism into a potential oncogenic process.

Interestingly, **anti-Lewis antibodies** have also been identified in **uninfected individuals and healthy control sera**, indicating that certain autoreactive antibodies may arise independently of *H. pylori* infection and could represent naturally occurring autoantibodies with limited pathogenic potential.

Table 3. *Helicobacter pylori* (*H.p.*)-mediated modulation of the adaptive immune response.

H.p. LPS enhances Th1 responses, with the increased release of interferon-gamma and interleukin-2 and the suppression of Th2 functions.
VacA causes the vacuolization of T cells, as well as restricted T cell stimulation through the activation of the NF-kB classical pathway.
H.p. infection expands Th17 cells, which, in turn, recruit macrophages for *H.p.* killing while activating Th1 cells through the secretion of IL-12 and IL-2.
VacA induces TREG cell differentiation in the gastric lamina propria, reprogramming dendritic cell activity, thus leading to the suppression of Th1 and Th17 cell responses and the progression of murine *H.p.* infection in *H.p.*-infected patients. TREG cells suppress cell memory response to *H.p.*, facilitating chronic infection.
H.p. infection triggers molecular mimicry, with anti-Lex antibodies cross-reacting with the gastric mucosa.
Anti-Lex IgM are protective, while anti-Lex IgG may contribute to *H.p.*-mediated gastropathy.

Trained immunity (TI) refers to the enhanced immune response and memory-like behavior of innate lymphoid cells (ILCs) and macrophages upon repeated exposure to the same pathogen. However, TI in response to *H. pylori* appears to be ineffective, as the bacterium suppresses immune activation during the later stages of infection.

Based on this, efforts have been made to restore TI during *H. pylori* infection. The weak ability of *H. pylori* lipopolysaccharide (LPS) to induce TI can be improved through monocyte priming, which enhances NF-κB translocation and promotes a stronger protective immune response. Additionally, *H. pylori* has been shown to alter lipid rafts in macrophages and natural killer (NK) cells, aiding immune evasion. Thus, targeting the interaction between *H. pylori* and lipid rafts may help reestablish TI.

In a double-blind, randomized clinical trial, patients with *H. pylori*–positive gastritis who received oral oat β-glucan supplementation showed reduced mucosal damage. The study suggested that β-glucan might enhance macrophage function and restore TI. In conclusion, targeting macrophage activity during *H. pylori* infection could serve as a potential therapeutic approach to counteract the bacterium's immune escape mechanisms.

The host immune response, however, can vary significantly depending on demographic and individual factors, as summarized in Table 4.

Table 4. A brief summary of demographic factors affecting the immune response in *H. pylori*-infected individuals.

Demographic Factors	Immune Response Characteristics
Age	- Younger individuals might show a more robust Th2 response, potentially leading to less severe disease. - Older individuals often have a Th1-dominant response associated with chronic inflammation and increased risk of complications like gastric cancer.
Gender	- Some studies suggest that females might have a stronger humoral (antibody-mediated) immune response. - However, gender-specific differences in immune response are not consistently reported.
Race/Ethnicity	- Differences in immune response can be observed among different ethnic groups, potentially due to genetic variations in immune genes. - For instance, certain ethnic groups might have higher rates of specific antibody classes or inflammatory markers.
Geographic Area	- The immune response varies by region, possibly due to differences in H. pylori strains, host genetics, and co-infections (like parasites). - In Africa, a Th2-dominant immune response has been noted, which might explain lower rates of gastric cancer despite high infection rates.
Socioeconomic Status	- Lower socioeconomic status is associated with earlier infection and potentially a less effective immune response due to chronic stress, malnutrition, or repeated infections.

Demographic Factors	Immune Response Characteristics
	- Higher status might correlate with better immune response due to better health care and living conditions.
Genetic Background	- Genetic polymorphisms in genes like IL-1β, TNF-α, and others can influence the inflammatory response and disease outcome. - Certain genotypes are linked to an increased risk of developing severe outcomes like gastric cancer.
Urban vs. Rural	- Urban environments might see different immune profiles due to different pathogen exposures, dietary habits, or environmental factors. - Rural settings with higher parasite co-infections might skew toward a Th2 response, potentially modulating H. pylori effects.
Nutritional Status	- Malnutrition can impair both innate and adaptive immune responses, leading to more severe or persistent infection. - Adequate nutrition supports a balanced immune response, possibly leading to better control of the infection.

Conclusions

During *Helicobacter pylori* infection, the modulation of the immune response varies widely, influenced by different bacterial components that can trigger contrasting reactions in host cells. Key pathogenetic factors include lipid A, CagA, VacA, and urease. Generally, *H. pylori* entry into the gastric environment activates the innate immune response through the phagocytic activity of neutrophils and macrophages, along with cytokine- and chemokine-mediated recruitment of adaptive immune cells, including T and B lymphocytes.

As the infection progresses, *H. pylori* evades immune surveillance by suppressing protective responses through several mechanisms—most notably, the activation of T regulatory (TREG) cells—which promotes bacterial persistence and chronic inflammation. Structurally, *H. pylori* lipid A displays lower endotoxic activity than lipid A from other Gram-negative bacteria, weakening host defenses. Moreover, the expression and variability of Lewis antigens within the O-polysaccharide chain of *H. pylori* LPS mimic host molecules, allowing the bacterium to remain undetected by the immune system.

Importantly, *H. pylori* infection is linked to neoplastic progression: chronic gastritis can lead to gastric epithelial cell apoptosis, intestinal metaplasia, and ultimately invasive gastric adenocarcinoma. Additionally, *H. pylori*–induced activation of NF-κB disrupts normal

lymphocyte function, contributing to autoimmune reactions and the development of gastric mucosa-associated lymphoid tissue (MALT) lymphoma.

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