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Review

The Role of the Immune Response to *Helicobacter pylori* Antigens and Its Relevance in Gastric Disorders

Luigi Santacroce [1,2,*], Skender Topi [2], Concetta Cafiero [3], Raffaele Palmirotta [1,2] and Emilio Jirillo [1]

[1] Interdisciplinary Department of Medicine, University of Bari "Aldo Moro", 70124 Bari, Italy; raffaele.palmirotta@uniba.it (R.P.); emilio.jirillo@uniba.it (E.J.)
[2] Department of Clinical Disciplines, University 'Alexander Xhuvani' of Elbasan, 3001 Elbasan, Albania; skender.topi@uniel.edu.al
[3] Medical Oncology, SG Moscati Hospital, 74010 Taranto, Italy; concettacafiero@gmail.com
* Correspondence: luigi.santacroce@uniba.it

Abstract: *Helicobacter pylori* (*H.p.*) is a Gram-negative bacterium endowed with gastric tropism. *H.p.* infection is widely spread throughout the world, accounting for various pathologies, such as peptic ulcer, gastric cancer, mucosa-associated lymphoid tissue lymphoma, and extra-gastric manifestations. This bacterium possesses several virulence factors, e.g., lipopolysaccharides (LPS), the toxins CagA and VacA, and adhesins, which elicit a robust immune response during the initial phase of the infection. Of note, the lipid A moiety of the LPS exhibits a lower endotoxic potency than that of other LPSs, thus facilitating infection through a mechanism of immune escape. *H.p.* colonization of the gastric mucosa induces an initial protective immune response with innate immune cells, e.g., neutrophils, monocytes, and macrophages, which engulf and kill bacteria. Moreover, the same cells, along with gastric epithelial cells, secrete cytokines and chemokines, which recruit T cells [T helper (h)1 and Th17 cells] to the site of infection, thus leading to *H.p.* eradication. In a large subset of individuals, the perturbation of such an immune equilibrium leads to a harmful response, with an expansion of T regulatory (TREG) cells, which suppress the protective immune response. In fact, TREG cells, via the production of interleukin (IL)-10, downregulate Th1- and Th17-related cytokines, thus allowing *H.p.* survival and the perpetuation of inflammation. As far as the humoral immune response is concerned, B cells, upon *H.p.* stimulation, produce autoreactive antibodies, and IgG anti-Le^x antibodies are harmful to the gastric mucosa. In this review, the structure and function of *H.p.* antigenic components and immune mechanisms elicited by this bacterium will be described in relation to gastric damage.

Keywords: *Helicobacter pylori*; gastropathy; immunity; immune escape; molecular mimicry; immune suppression

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1. Introduction

Helicobacter pylori (*H.p.*) is a microaerophilic, spiral-shaped, Gram-negative bacterium that colonizes the gastric mucosa in about 50% of the world's population [1]. Its presence is often associated with gastritis, duodenal ulcers, mucosal-associated lymphoid tissue (MALT), and related cancers (MALTomas), as well as extra-gastric pathologies, because of its ability to perform the so-called "immune escape", which allows it to survive in the hostile gastric milieu [2,3].

The pathogenetic mechanisms elicited by *H.p.* infection are different. In this respect, *H.p.* produces urease, which enables its survival in the low-pH acidic environment of the

stomach [4]. Then, *H.p.*, thanks to its flagella, moves through the mucosa layer, reaching the gastric epithelium, where it adheres to host cell receptors, ultimately colonizing the mucosa [5]. Upon firm attachment, *H.p.* employs virulence factors to perturb host cell signaling; among these, cytotoxin-associated gene A (Cag A) and vacuolar cytotoxin A (VacA) represent toxins that contribute to gastric pathology [6,7]. CagA dysregulates mitogen-activated protein kinase (MAPK) and phosphatidyl inositol s-kinase (PI3K) pathways, leading to morphological changes in host cells, the suppression of the protective immune response, and carcinogenesis [8]. On the other hand, VacA forms channels and pores in the host cell membranes, altering their permeability, along with mitochondrial stress, autophagy, apoptosis, and the suppression of effector T cells [9,10].

In conclusion, both Cag A and Vac A induce and maintain a chronic inflammatory status of the gastric mucosa, also favoring immune escape.

There is evidence that *H.p.* possesses a less toxic lipopolysaccharide (LPS) or endotoxin in its outer cell wall membrane in comparison with other Gram-negative bacteria, e.g., *Escherichia* (*E.*) *coli* and *Salmonella* [11]. In detail, the toxic moiety of the entire LPS molecule, lipid A, exhibits certain structural modifications, which accounts for its lower endotoxicity [12]. In fact, lipid A consists of tretraacyl lipid A, with long acyl chains of 16 to 18 carbons, which are responsible for the reduced endotoxic potency. This fact favors the immune escape of *H.p.* since its lipid A weakly activates certain innate receptors, i.e., toll-like receptors (TLRs), on the surface of gastric epithelial cells and local neutrophils, monocytes, and macrophages, ultimately impeding a robust host protective immune response [13,14].

The gastric immune response against *H.p.* colonization is biphasic. In fact, at the initial stage of infection, antigenic components of the bacterium trigger a potent innate immune response, which involves neutrophils, monocytes, and macrophages that can engulf bacteria, on the one hand, and, on the other hand, release pro-inflammatory cytokines and chemokines [15]. In this framework, interleukin (IL)-8 is a chemokine that recruits other monocytes and macrophages, as well as T and B cells, to the major site of gastric infections, promoting protective inflammatory conditions. However, the interruption of the immune homeostasis under the persistent antigenic pressure exerted by *H.p.* may lead to a shift in the immune response toward a condition of tolerance, with increased activation of T regulatory (TREG) cells, which abrogate host protection [16]. Moreover, *H.p.* infection exerts an inhibitory effect on epidermal growth factor beta and transforming growth factor beta, which are involved in the mechanisms of gastric mucosa repair [17].

These are some of the major mechanisms of immune escape adopted by *H.p.* If the *H.p.*-mediated inflammation becomes too much persistent the risk of gastric carcinogenesis is very high [18].

The present review will deal with the immunomodulatory mechanisms exerted by *H.p.* Then, antigenic components of *H.p.*, including LPS, Cag A, and VacA, will be described in relation to their ability to modulate immune responsiveness during *H.p.* infection, thus leading to a condition of chronic gastritis.

2. Major Antigenic Components of *H.p.*

Compared to other Gram-negative bacteria, *H.p.* LPS comprises the O-polysaccharide chain, the core, and the innermost part of the molecule, lipid A. Quite importantly, lipid A exhibits a lower potency than lipid A from other Gram-negative bacteria [12,19]. Lipid A fatty acids are longer than those present in lipid A from other Gram-negative bacteria, with tetra-acyl lipid A as the predominant structure [20]. Tetra-acyl lipid A has acyl chains that are 16 to 18 carbons long. An enzyme named Jhp0634, which is an outer membrane deacylase, removes the acyl chains at the 3′ position [21].

Conversely, lipid A from *Salmonella* (*S.*) *minnesota* and *E. coli* exhibits a fatty acid composition and degree of acylation that are essential for biological and toxic activities [22]. On these grounds, evidence has been provided that *H.p.* lipid A exhibits a lower ability to induce the release of cytokines, nitric oxide (NO), and prostaglandin E2, express selectins, activate natural killer (NK) cells, and downregulate TREG cell activity [23].

In conclusion, in view of the above-cited characteristics, *H.p.* can evade host defenses, contributing to gastric infection perpetuation.

H.p. O-polysaccharide antigen is strongly conserved but fucosylated, thus mimicking human Lewis molecules and other related blood-group antigens, i.e., Le^x, Le^y, Le^a, Le^b, Le^c, sialyl-Le^x, and H-1 antigen [24,25]. The inactivation of the *H.p.* Le^x and Le^y determinants limits the in vivo colonization of *H.p.* in mice [26]. Of note, the expression of Le^x or Le^y determinants of the *H.p.* O-polysaccharide chain supports the concept of molecular mimicry, with the induction of potentially anti-Le^x and anti-Ley autoreactive antibodies, which can provoke gastric damage [27]. In this last respect, the *H.p.* Le^x structure is recognized by the gastric receptor galectin-3 [28].

H.p.-mediated disease depends on the expression of two virulence factors, the proteins CagA and VacA [29].

CagA is expressed by 70% of strains and produces the type IV secretion system (TIVSS), with the generation of a pilus, which allows its injection into host cells through binding to the beta 1 receptor [30]. TIVSS-positive strains of *H.p.* are more prone to cause gastric chronic infections and cancer in humans [31]. Then, CagA undergoes tyrosine phosphorylation, with the activation of the MAPK and PI3K pathways, leading to abnormal host responses, as described in the next section of the present review [32].

With special reference to VacA, its secreted 88 kDa promoter consists of an N-terminal p33 domain and a C-terminal p55 domain, linked by a flexible loop, which is sensitive to in vitro proteolysis [33]. The p33 domain is responsible for pore-forming activity, while the p55 domain is essential for the receptor binding to host cells [34]. In detail, the vacuolating activity of VacA causes cleavage of intercellular adhesion proteins, e.g., E-cadherin, occludin, and claudin-8, ultimately altering the integrity of the gastric barrier [5].

H.p. outer membrane vesicles (OMVs) are bacterial components, ranging between 20 and 30 nm, which the bacterium disseminates for the long-distance delivery of virulence factors [35]. *H.p.* OMVs mainly contain phospholipids, LPS, CagA, VacA, and various adhesins, e.g., SabA, BabA, AlpA, AlpB, OipA, and Hop2, and enzymes, like urease, catalase, and serin protease [36]. *H.p.* OMVs have been shown to form biofilms on human gastric mucosa, thus protecting bacteria from the host immune response and antimicrobials [37]. Once internalized by gastric epithelial cells, *H.p.* OMVs release IL-8, which recruits immune cells to the gastric mucosa, e.g., T cells, B cells, NK cells, and monocytes [38,39]. These cells infiltrate the gastric lamina propria, promote inflammation, and exert suppressive functions, abrogating the protective immune response.

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

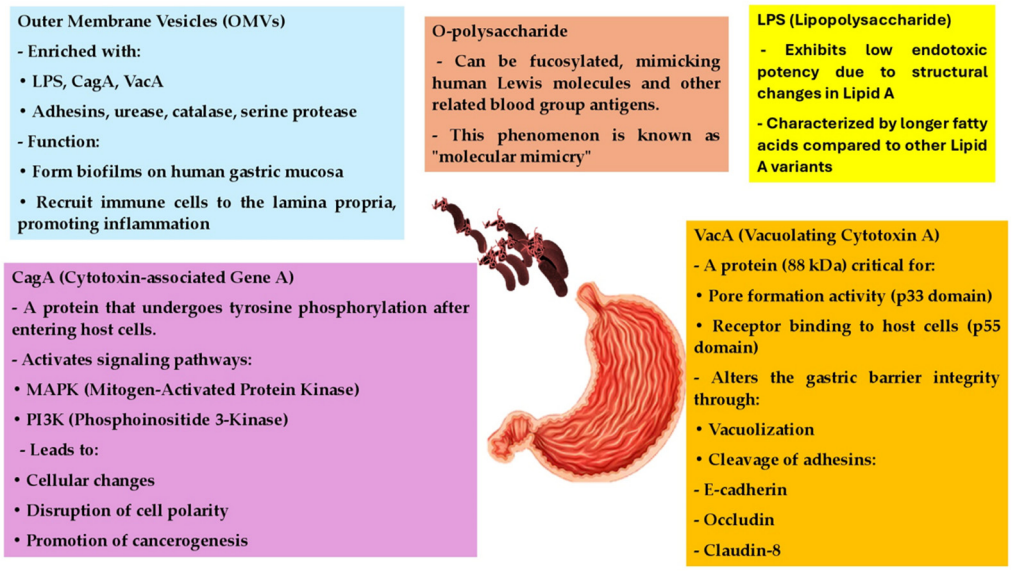

Figure 1. Antigenic components of *Helicobacter pylori* (*H.p.*).

3. Pathogenesis of *H.p.* Infection

H.p. adhesion to the gastric mucosa represents the first step of infection, with bacterial chemotaxis to the TlpB receptor on target cells [40]. The TlpB family is triggered by signals released by urea, lactic acid, reactive oxygen species (ROS), and gastric juice. *H.p.* motility depends on flagella, which allow bacteria to swim through the mucous layer, finally adhering and colonizing the gastric mucosa [5].

Furthermore, *H.p.* adherence is enhanced by the formation of biofilms embedded in the extracellular matrix, which offer protection to the bacterium against host defenses and antibiotic therapy [41]. Once attached to the mucosa, *H.p.* exploits its virulence factors to modulate the host's protective response.

CagA, which undergoes tyrosine phosphorylation, leads to an aberrant activation of the MAPK and PI3K pathways, with morphological changes in host cells, the disruption of cellular polarity, the release of cytokines and chemokines, and the initiation of carcinogenesis [42,43].

VacA forms pores and channels in the gastric cell membrane, with an increase in permeability [44]. Furthermore, VacA induces either pro-apoptotic or anti-apoptotic effects, autophagy, and inflammation via cytokine release, inflammasome activation, and T cell proliferation [7]. Of note, CagA and VacA collaborate in the dysregulation of the nuclear factor of activated 1 cell signaling, with enhanced expression of the gene *p21*, changes in the cell cycle, differentiation, and the promotion of carcinogenesis [7].

Urease is largely produced by *H.p.*, thus allowing its survival in the low-pH acidic gastric milieu, breaking down the urea into ammonia and carbon dioxide, with the formation of a pH-neutral environment [4].

In the context of the gastric mucosa, *H.p.* activates pattern recognition receptors (PPRs); among these, TLRs and nucleotide-binding oligomerization domain-like receptors (NLRs) are the major receptors.

TLRs are transmembrane proteins that recognize microbial components on antigen-presenting cells, such as dendritic cells and macrophages, linking the innate to the adaptive immune response [45]. The activation of NLRs by pathogens promotes the formation of inflammasomes, which convey the presence of bacterial antigens to the immune network through the system of caspases and the release of pro-inflammatory cytokines, e.g., IL-1 beta and IL-8 [46].

H.p. LPS binds to TLRs expressed on epithelial cells, monocytes, and macrophages, with the translocation of NF-kB to the nucleus and the release of pro-inflammatory cytokines, e.g., IL-1 beta, TNF-alpha, and IL-8 [47]. TLR7, TLR8, and TLR9 recognize *H.p.* DNA and RNA, while TLR2 and TLR5 recognize cell wall components and flagellin [48]. Of note, in *H.p.* infected individuals' gene polymorphisms of TLR1 and TLR10 are associated with an increased risk of gastric cancer [48]. Also, the PPR-mediated recruitment of MyD88 and TRIF activates downstream signals, e.g., NF-kB, MAPKS, and interferon regulatory factors, which lead to the release of pro-inflammatory cytokines, IL-1 beta, and TNF-alpha, with the recruitment of neutrophils and monocytes promoting host defenses against *H.p.* organisms [49].

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.

4. *H.p.*-Mediated Modulation of the Innate Immune Response

The immune response elicited by *H.p.* begins with the recognition of pathogen-associated molecular patterns (PAMPs) by PRRs, e.g., TLRs, NLRs, C-type lectin receptors, and retinoic acid-inducible gene (RIG)-I-like receptors (RLRs) expressed on innate immune cells or gastric epithelial cells [50]. *H.p.* lipid A preferentially binds to TLR4; however, it leads to a weak inflammatory response [51]. In fact, in vitro lipid A dephosphorylation with the removal of the 1′ and 4′ phosphate groups reduces the potency of the entire molecule, mimicking the in vivo effects of *H.p.* lipid A. In this framework, evidence has been provided that TLR4 alone or with MD-2 mutations is scarcely activated by *H.p.* LPS, thus suggesting another method of receptor evasion facilitated by the bacterium [52]. With special reference to TLR2, there is evidence that this receptor becomes activated in the presence of *H.p.* neutrophil-activating protein, with the release of the pro-inflammatory chemokine IL-8 [53]. In addition to the low antigenicity of *H.p.* LPS, its flagellin is also less potent in activating TLR5 due to mutations of R89T, L93K, and E114D [54].

RLRs are activated during *H.p.* infection through the suppression of the STING and RIG-I pathways, thus leading to Th17-mediated inflammation, with increased expression of Trim 30a [55].

NLRP3 inflammasome is activated upon TLR2 recognition of *H.p.*, with the production of IL-1beta and T cell differentiation toward the TREG cell subset with the suppression of the protective host immune response against *H.p.* [56].

H.p. infection has been shown to negatively influence macrophage function. In this respect, *H.p.* LPS binding to CD14 and TLR4 triggers the release of pro-inflammatory cytokines, such as IL-1 beta, IL-6, and TNF-alpha, through the activation of NF-kB, thus offering protection to the host [57]. At the same time, such a process inhibits the transmission of the phagocytic signals and endocytosis of macrophages, interfering with PI3K/Akt and JAK/SAT signaling pathways, thus promoting *H.p.* infection. This fact indicates that

H.p. can elicit opposite host responses, which can be protective or harmful according to the immune homeostasis at that given moment. Furthermore, CagA impairs macrophage phagocytosis by binding to E-cadherin and beta1 integrin or hampering the fusion of the phagosome with the lysosome, thus preventing the formation of an acidic milieu [58,59]. In addition, *H.p.* OMPs, BabA, and Sab A inhibit macrophage cytoskeleton and function with the abrogation of phagolysosome formation [60]. It is worth noting that the binding of *H.p.* LPS, CagA, and VacA to macrophages increases intracellular calcium, preventing phagocytosis and leading to mitochondrial dysfunction and apoptosis [61,62].

H.p. CagA influences the equilibrium between M1 and M2 macrophages through the induction of heme-oxygenase-1 (HMOX 1, HO-1) [63]. In this respect, M1 macrophages eradicate pathogens via ROS production and the recruitment of Th1 and NK cells [64]. Conversely, M2 macrophages are characterized by the production of the anti-inflammatory cytokine IL-10 and the low production of IL-12, with reduced activation of Th1 cells [64]. In detail, HO-1 inhibits M1 macrophages, shifting the balance toward M2 macrophages, which suppress the protective response against *H.p.*, allowing for bacterial survival [65,66]. In chronic gastritis, the *H.p.*-mediated generation of nitric oxide (NO) inhibits the transition from M1 to M2 macrophages, while NO release suppression allows for reprogramming toward the M2 phenotype [67]. In this framework, *H.p.* infection induces arginase 2 expression in macrophages, with a reduction in L-arginine and NO-mediated bactericidal activity [68], as well as impairment of Th1/Th17 cell differentiation; thus, *H.p.* escape is favored during chronic infection [69]. Moreover, ornithine decarboxylase is upregulated by *H.p.* infection with a shift toward the M1 macrophage phenotype [70]. Also, cystathionine gamma-lyase (CTH) is a regulator of the M1/M2 balance, and in *cth* gene knockout mice infected with *H.p.*, there is a shift toward the M1 phenotype [71].

Innate lymphoid cells (ILCs) are also involved during *H.p.* infection. In this respect, ILCs can be divided into three main groups, with ILC1s mostly consisting of NK cells, ILC2s characterized by the secretion of Th2-related cytokines, e.g., Il-5 and IL-13, and ILC3s consisting of lymphoid tissue inducer cells, natural cytotoxic receptor (NCR)+, and NCR-ILC3s [72]. NK cells are large granular lymphocytes, and their function is to kill target cells infected by viruses, bacteria, and tumor cells [73]. In *H.p*-infected individuals, CD8-CD16-CD56+ bright NK cells directly respond to bacteria with the secretion of IFN-gamma or indirectly via cytokine activation [74,75]. However, *H.p.* LPS downregulates NK cell cytotoxicity, with lower production of IFN-gamma, IL-2, and IL-10 by peripheral blood lymphocytes from *H.p.*-infected individuals [76].

Furthermore, during *H.p.* infection, ILC3s located in the gut generate IL-22 and IL-17, preventing systemic inflammation [77].

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.

Table 2. *Cont.*

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.

5. *H.p.*-Mediated Modulation of the Adaptive Immune Response

The effects of *H.p.* on the adaptive immune response have intensively been investigated.

Experimentally, mice administered with *H.p.* preparations enriched in LPS and CagA elicited a robust Th1 response with suppression of Th2 activity [78]. In detail, *H.p.* LPS enhanced IFN-gamma and IL-12 secretion with suppression of IL-2, which is crucial for Th2 responses to occur [79]. Conversely, Lewis-positive *H.p.* strains, which bind to DC-sign C-type lectin expressed on gastric T cells, abrogated Th1 cell development, although this was not the case for Lewis-negative *H.p.* variants [80]. Furthermore, VacA binds to the beta2 integrin subunit CD18, altering cell morphology and suppressing T cell response [81].

At the same time, VacA causes the vacuolization of T cells, interacting with LAF-1 [82]. Conversely, VacA activated NF-kB on T cells via the classical pathway, thereby inducing an inflammatory immune response [83].

During *H.p.* infection, the release of IL-17 by Th17 cells occurs, with the engulfment and killing of *H.p.* organisms through TLR4 and TLR2 activation [78,84]. In addition, Th17 cells secrete IL-12 and IL-2, with the activation of Th1 cells and production of IFN-gamma and TNF-alpha [85]. Moreover, neutrophil extracellular traps can induce the differentiation of Th17 cells through TLR2 [86]. These data clarify how *H.p.* affords protection to the host through a network of cytokines, including IL-2, IL-12, and Il-17 secreted by Th1 and Th17 cells, respectively. However, in the later phase of Th17 development, Il-23, which is secreted by gastric epithelial cells, and the CagA-mediated downregulation of B7-H2 expression tend to diminish the activity of T effector cells, including Th17 cells [87,88]. The decline of Th17 cells paves the way for TREG cell surgency. In fact, VacA targets myeloid cells in the gastric lamina propria, inducing the differentiation of CD25+Foxp3+ TREG cells, which suppress protective inflammation via the release of IL-10 [89,90]. Experimentally, athymic mice transfected with CD25(-) lymph node cells underwent a reduced colonization of *H.p.* in the stomach in comparison with the group transfected with CD25(+) lymph node cells [91]. The same authors reported that spleen cells from mice receiving CD25(-) lymph node cells produced higher levels of IFN-gamma under *H.p.* stimulation, with massive infiltration of macrophages and T cells in the gastric mucosa, thus contributing to *H.p.* eradication. Similarly, an increase in peripheral blood CD25(+) Treg cells was observed following their in vitro pretreatment with *H.p.* and/or *H.p.* stimulated AGS cells [10]. Clinically, in *H.p.*-infected patients, elevated numbers of peripheral TREG cells were detected, with the suppression of T cell memory response to *H.p.*, thus facilitating chronic infection [92].

As far as other methods of protective immunity suppression during *H.p.* infection are concerned, suppressors of cytokine signaling (SOCs) proteins are released during *H.p.* infection, interacting with STAT molecules at certain phosphorylated regions of the cytokine receptors [93]. SOCs have been shown to play a role in *H.p.* escape and chronic gastritis development [94].

Conclusively, *H.p.* skews the Th17/TREG cell balance toward TREG cell responsiveness, thus abrogating *H.p.* eradication [95].

With special reference to B cell activity during *H.p.* infection, *H.p.* triggers autoreactive antibodies in almost 50% of *H.p.*+ individuals, which decrease following bacterium eradication. Molecular mimicry responsible for autoreactivity depends on various antigens, including *H.p.* heat shock protein 60, Le antigens, and H+- and K+-ATPase [96]. Anti-Lewis antibodies can cross-react with the gastric mucosa, and anti-Le^x antibodies are the most frequent of all. There is evidence that anti-Le^x IgM is protective, while anti-Le^x IgG may contribute to *H.p.*-mediated gastropathy [97]. In *H.p.*-related duodenal ulcers, IgG antibody responds to smooth forms of *H.p.* LPS was more elevated than against rough (R) forms [98]. In addition to IgG, IgA antibodies against LPS in R forms of *H.p.* have been detected, thus suggesting an unmasking of the core structure during *H.p.* infection. However, such overstimulation of B cell activity during *H.p.* infection can induce the accumulation of activated lymph cells in gastric lamina propria, leading to MALToma [99,100].

Conversely, anti-Lewis antibodies have been found in normal sera and non-infected controls, thus indicating that autoreactive antibodies are unrelated to infection with *H.p.* [101].

The mechanisms of adaptive immunity modulation during *H.p.* infection are illustrated in Table 3.

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.

6. The Concept of Trained Immunity During *H.p.* Infection

Trained immunity (TI) involves an enhanced immune response and memory-like characteristics of ILCs and macrophages upon subsequent contact with the same pathogen [102]. TI in response to *H.p.* stimulus seems to be ineffective since the bacterium tends to suppress the immune response during the later phase of infection [103].

On these bases, attempts have been made to recover TI during *H.p.* infection. In this respect, the weak potency of *H.p.* LPS to induce TI has been upregulated by monocyte priming by *H.p.* LPS, with NF-kB translocation and robust protective immune response [104,105]. Furthermore, there is evidence that *H.p.* can modify lipid rafts in macrophages and NK cells, thus promoting bacterium immune evasion [106]. Therefore, the interaction of *H.p.* with lipid rafts may represent a target for the recovery of TI.

In a double-blind, randomized clinical trial, *H.p.*+ gastritis patients underwent oral-oat beta-glucan dietary treatment with reduced mucosal damage [107]. The same authors hypothesized a β-glucan-mediated improvement of macrophage function with recovery of TI. Conclusively, targeting macrophage function during *H.p.* infection may represent a potential therapeutic tool to interrupt the mechanism of immune escape adopted by this bacterium.

Anyway, the host immune response can greatly vary based on several demographic conditions, 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. - 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.

The specific immune responses against *H. pylori* can vary based on a lot of interacting factors, including specific *H.p.* strains, host genetics, environmental conditions, and concurrent infections [108–112].

7. Conclusions

During *H.p.* infection, the tuning of the immune response is quite variable, depending on various bacterial components, which can solicit opposite reactions by host cells. This is the case for lipid A, CagA, VacA, and urease as major pathogenetic factors. In general terms, the penetration of *H.p.* into the gastric milieu generates a prompt activation of the host innate immune response through phagocytic activities of neutrophils and macrophages, as well as the cytokine- and chemokine-dependent recruitment of adaptive immune cells and T and B lymphocytes. In the later stage of infection, *H.p.* escapes from immunosurveillance,

suppressing the protective immune response with various mechanisms, including the activation of TREG cells, thus facilitating bacterial growth and the perpetuation of the inflammation. Structurally, *H.p.* lipid A possesses lower endotoxic activity in comparison with lipid A from other Gram-negative bacteria, thereby reducing host protection against *H.p.* Furthermore, the expression and variation of Lewis determinants in the context of the O-polysaccharide of *H.p.* LPS mimic host components, rendering bacteria invisible to the immune system. In this framework, emphasis should be placed on the neoplastic evolution of *H.p.* infection. In fact, chronic gastritis is followed by gastric epithelial cell apoptosis with intestinal metaplasia and, eventually, invasive gastric adenocarcinoma. On the other hand, the *H.p.*-mediated activation of the NF-kB alters the normal function of lymphocytes, which may lead to autoimmunity and gastric mucosa-associated lymphoid tissue lymphoma.

Improved knowledge of the above-cited immune events may aid in the design of novel therapies for the prevention and treatment of *H.p.*-related disease.

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Abbreviations

CagA	Cytotoxin-associated gene A
IFN	Interferon
IL	Interleukin
ILCs	Innate lymphoid cells
LPS	Lipopolysaccharides
MAPK	Mitogen-activated protein kinase
NCR	Natural cytotoxic receptor
NK	Natural killer
NLRs	Nucleotide-binding oligomerization domain-like receptors
NO	Nitric oxide
OMVs	Outer membrane vesicles
PRRs	Pattern recognition receptors
PI3K	Phosphatidyl-3 inositol-3 kinase
RLRs	Retinoic acid-inducible gene-1 (Rig-1)-like receptors
R	Rough
ROS	Reactive oxygen species
TIVSS	Type IV secretion system
TNF	Tumor necrosis factor
VacA	Vacuolar cytotoxin A
TREG	T regulatory

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