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TOPIC HIGHLIGHT

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Structural modifications of *Helicobacter pylori* lipopolysaccharide: An idea for how to live in peace

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Abstract

In this review, we discuss the findings and concepts underlying the "persistence mechanisms" of *Helicobacter pylori* (*H. pylori*), a spiral-shaped, Gram-negative rod bacterium that was discovered as a gastric pathogen by Marshall and Warren in 1984. *H. pylori* colonizes the gastric mucosa of nearly half of the human population. Infections appear in early childhood and, if not treated, persist for life. The presence or absence of symptoms and their severity depend on multiple bacterial components, host susceptibility and environmental factors, which allow *H. pylori* to switch between pathogenicity and commensalism. Many studies have shown that *H. pylori* components may facilitate the colonization process and the immune response of the host during the course of *H. pylori* infection. These *H. pylori*-driven interactions might result from positive or negative modulation. Among the negative immunomodulators, a prominent position is occupied by a vacuolating toxin A (VacA) and cytotoxin-associated gene A (CagA) protein. However, in light of the recent studies that are presented in this review, it is necessary to enrich this panel with *H. pylori* lipopolysaccharide (LPS). Together with CagA and VacA, LPS suppresses the elimination of *H. pylori* bacteria from the gastric mucosa by interfering with the activity of innate and adaptive immune cells, diminishing the inflammatory response, and affecting the adaptive T lymphocyte response, thus facilitating the development of chronic infections. The complex strategy of *H. pylori* bacteria for survival in the gastric mucosa of the host involves both structural modifications of LPS lipid A to diminish its endotoxic properties and the expression and variation of Lewis determinants, arranged in O-specific chains of *H. pylori* LPS. By mimicking host components, this phenomenon leaves these bacteria "invisible" to immune cells. Together, these mechanisms allow *H. pylori* to survive and live for many years within their hosts.

Key words: *Helicobacter pylori*; Lipopolysaccharide; Immune response; Adaptation; Inflammation

Core tip: *Helicobacter pylori* (*H. pylori*), a Gram-negative bacterium, colonizes the gastric mucosa of at least half of the human population and possesses a unique lipopolysaccharide (LPS) structure. According to recent studies, this structure contributes to the immunomodulatory properties of LPS. The structural rearrangements of *H. pylori* LPS, especially in relation to the lipid A and O side chains, result in a unique pattern of interactions between the bacterium and the host. In this review, we report and discuss the actual findings underlying the LPS-driven "persistence mechanisms" of *H. pylori*, explaining how structural modifications may allow these bacteria to "live in peace" within a human host.

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INTRODUCTION

In this review, we discuss the findings and concepts underlying the "persistence mechanisms" of *Helicobacter pylori* (*H. pylori*), a human pathogen colonizing the gastric mucosa. We focus on aspects concerning the structure, bioactivity, and immunomodulatory properties of *H. pylori* lipopolysaccharide (LPS) and its contribution to the development of chronic gastritis. Today, we know that LPS is the main outer membrane component of Gram-negative bacteria and that LPS has strong immunostimulatory and inflammatory capacities. Recent years have provided new insights into the *H. pylori* LPS structure and the receptors of the innate immune system that are involved in its recognition and signal transduction pathways. These new data allow a more precise definition of the harmful and beneficial effects of *H. pylori* LPS. There is a growing number of theories suggesting that *H. pylori* LPS has evolved during the co-existence of these bacteria with human hosts since the migrations out of Africa 60000 years ago, enabling these bacteria "to live in peace"[1].

HELICOBACTER PYLORI: BETWEEN PATHOGENICITY AND COMMENSALISM

H. pylori is a spiral-shaped, Gram-negative rod bacteria that was discovered as a gastric pathogen by Marshall *et al*[2]. *H. pylori* colonizes the gastric mucosa of nearly half of the human population. Infections appear in early childhood and, if not treated, persist for life[3]. Disease development depends on multiple bacterial virulence components, host susceptibility, and environmental factors[4]. A characteristic symptom of *H. pylori* infection is an excessive inflammatory response, which results in the development of pathological processes in the gastric epithelium, such as erosions, ulcers, changes in cell phenotype, excessive cell proliferation, and the secretion of proinflammatory cytokines[5-7]. The balance of bacterial factors and the host inflammatory response to *H. pylori* infection determines the outcome of the disease[8]. Most *H. pylori*-infected individuals (80% to 90%) remain clinically asymptomatic throughout their lifespan. In most cases, *H. pylori* colonizes the stomach for many decades before symptoms appear, which distinguishes this bacterium from bacterial pathogens that cause acute infections. However, even in asymptomatic subjects, *H. pylori* induces histological gastritis, due to the infiltration of the gastric mucosa by immune cells[9]. Approximately 10% of infected subjects develop symptomatic gastritis, peptic ulcer, or even gastric cancer. Despite the high prevalence of *H. pylori* infection in Africa and South Asia, the incidence of gastric cancer in those areas is much lower than in other regions. Such geographic differences in pathology can be explained in part by the presence of different types of *H. pylori* virulence factors[4,10-13]. Many studies have been performed to define what makes *H. pylori* a pathogen and, at the same time, why so many people do not suffer due to infection. Generally, penetration of *H. pylori* through the gastric mucosa results in the recruitment of host immune defenses to the site of infection and the development of acute inflammation. If the course of events is favorable to the host, the bacteria are eliminated, and healing begins. However, when acute inflammation fails to fight the infection, a chronic inflammatory response occurs. Among several mediators engaged in propagating gastric inflammation after *H. pylori* infection, cyclooxygenase-2[14], together with reactive oxygen species (ROS) and reactive nitrogen species (RNS)[15] might be the principal ones. Excessive ROS/RNS production correlates well with histopathological mucosal damage and with bacterial load[14,15]. The permanent recruitment of inflammatory cells to infectious foci results in progressive tissue damage. Asymptomatic *H. pylori*-infected individuals likely develop very weak gastric inflammation in response to *H. pylori*. In such conditions, the bacteria are not eliminated. A type of balance is created between the microbes and the host, which limits the recruitment of immune cells and prevents the development of gastric pathologies.

It is known that *H. pylori* is a genetically diverse species[5,7,8,16]. *H. pylori* strains isolated from different hosts possess various virulence capacities, and their genetic diversity may also appear within the gastric niche of a single human host. Most *H. pylori*-related diseases depend on the expression of specific protein virulence factors, such as cytotoxin-associated gene A (CagA) and vacuolating cytotoxin A (VacA)[7]. A recent study on *H. pylori*-host protein interactions confirmed that the type IV secretion system (TIVSS) can translocate CagA to gastric epithelial cells using human β1 integrin as a receptor[17]. *H. pylori* strains that are positive for the Cag TIVSS more successfully cause chronic infections in humans. In contrast, it has been observed that the activity of the TIVSS system may limit *H. pylori* colonization. The study in a mouse model has shown that an exchange of DNA between genetically heterogeneous *H. pylori* strains may support chronic colonization[18,19]. Other well-characterized *H. pylori* virulence factors include urease[20,21] and several types of outer membrane proteins, such as Hop proteins (Hsp70/Hsp90-organizing Hsp)[22] and blood antigen-binding adhesins[23]. However, the panel of *H. pylori* proteins is very complex and, as shown in a proteomics study, includes over 1200 compounds[24,25]. The role of the majority of these proteins in the course of *H. pylori*-related diseases needs to be clarified. It is interesting that different *H. pylori* proteins may interact with various host molecules and be involved in numerous pathogenic signaling pathways.

Key findings

H. pylori demonstrates high affinity to the gastric mucosa and is well adapted to live in the acidic environment of the stomach. In general, the interactions of *H. pylori* with host cells resemble a lifelong homeostasis, but in certain patients, these microbes cause pathological changes, such as ulcers or gastric cancers. It is not clear why certain patients remain asymptomatic, whereas others develop illness. Recently, both bacterial virulence factors and host susceptibility have been recognized as contributors to *H. pylori* pathogenicity.

UNIQUE STRUCTURAL AND BIOLOGICAL FEATURES OF *H. PYLORI* LPS - A KEY PLAYER IN THE PERSISTENCE STRATEGY

Although *H. pylori,* as a gastric pathogen, expresses several unquestionable virulence factors that are related to the cytotoxicity of this bacterium, its most potent feature is the ability to persist for years within the gastric epithelium of the host. This unique, adaptive property occurs due to a complex mechanism of *H. pylori* colonization and persistence, which is mediated by proteins, glycoconjugates, and lipids exposed on the surface of this bacterium. Well-characterized adhesins in *H. pylori* include blood antigen-binding adhesin (BabA), which interacts with the host's Lewis^{b} (Le^{b}), and sialic acid-binding adhesin, which binds sialylated Lewis^{X} (Le^{X}). There are many other *H. pylori* adhesion molecules, such as hemagglutinin, which interacts with sialic acid exposed on human tissues, and less-characterized adhesion molecules that interact with host extracellular matrix (ECM) molecules[12,23,26,27]. Among *H. pylori* virulence factors, LPS plays a special role due to its unique structural and biological properties, which differ from those of the LPSs typical of other Gram-negative bacteria. In general, these unique features concern modifications of lipid A, resulting in a reduction in the endotoxic and proinflammatory properties of *H. pylori* LPS[28,29] and the expression of O chains. These chains are structurally related to Lewis blood-group antigens, which are also expressed by human cells. This phenomenon, called molecular mimicry, most likely makes these pathogens less sensitive to recognition by the immune cells of the host[30]. The direct cytotoxic effect of *H. pylori* LPS on immune cells and epithelial as well as endothelial barriers and its immunomodulatory activity, mediated through different cytokines, are being investigated.

General structure of bacterial LPSs: A summary

Bacterial LPSs are described as heat-stable, non-protein, endotoxic cell wall components of Gram-negative bacteria that consist of conserved and highly variable regions[31,32]. Conserved parts of LPS are shared between various bacterial species and are critical for cell survival. In contrast, the variable regions of LPS are not essential for the existence of bacteria but promote evolutionary variations, which are crucial for the adaptation of microbes to the host or environment. In general, the structures of LPSs from various bacterial species and serotypes of Gram-negative bacteria are similar. These amphiphilic molecules contain two parts: a hydrophilic polysaccharide and lipid A, which constitutes a covalently bound hydrophobic lipid component. The polysaccharide moiety contains a core region and an *O*-specific chain, with a sequence of repeating units of identical polysaccharides, which are composed of several sugar monomers. Due to the great variety of monosaccharides occurring in the *O*-specific chain, this region of LPS is unique to each endotoxin and characterizes the serotype. The core region is less variable and is subdivided into outer and inner cores. The outer core may contain different sugar moieties: *D*-glucose, *D*-galactose, 2-amino-2-deoxy-*D*-galactose, and 2-amino-2-deoxy-*D*-galactose. The inner core contains 2-keto-3-deoxy-octulosonic acid (Kdo) and heptose residues, which are phosphorylated. Lipid A is known as the bioactive center of LPS and is composed of 1,6-linked *D*-glucosamine disaccharide, which is phosphorylated and possesses up to six acyl residues. There are differences in the length, position, and number of fatty acids. Lipid A is responsible for the endotoxic properties of LPS[32], and its bioactivity is defined as cytokine-inducing capacity. The minimal requirements for this activity include the presence of a molecule composed of two *gluco*-configurated hexosamine residues, two phosphate groups, and six fatty acids, as in lipid A of *Escherichia coli* (*E. coli*), which has been established as standard LPS (Figure 1)[33]. Modifications in the chemical structure of LPS, such as different phosphorylation or acylation patterns of hexosamine disaccharide, result in a varied ability to induce monokine production by immune cells. Endotoxicity is usually caused by monomeric LPS molecules, although at a higher concentration, the physical structure of LPS is also crucial for its bioactivity[34].

Lipid A of H. pylori LPS: A weak bioactive center

Similarly to other Gram-negative bacteria, *H. pylori* contains a cell envelope composed of poly- or oligosaccharides that are covalently linked to lipid A of LPS. Fresh clinical isolates produce a high-molecular-weight, smooth LPS with an O-antigen, which, in an *in vitro* culture, may convert into a rough form without the O side chain[35,36]. Lipid A of *H. pylori* LPS has a unique structure and lower biological activity compared with lipid A from other bacteria[28,29]. Probably it evolved due to adaptation to long-term infections in the gastric milieu. Structural analysis of *H. pylori* lipid A of the rough and smooth types has indicated that these lipids contain fatty acids that are longer than those present in lipid A of enterobacterial species. The predominant form is tetraacyl lipid A, with long acyl chains of 16 to 18 carbons and underphosphorylation, which are unusual properties for *H. pylori* lipid A (Figure 1)[34,37]. Studies on reference lipid A from *Salmonella minnesota* and *E. coli* have shown that specific phosphorylation patterns and fatty acid compositions and a particular degree of ac-

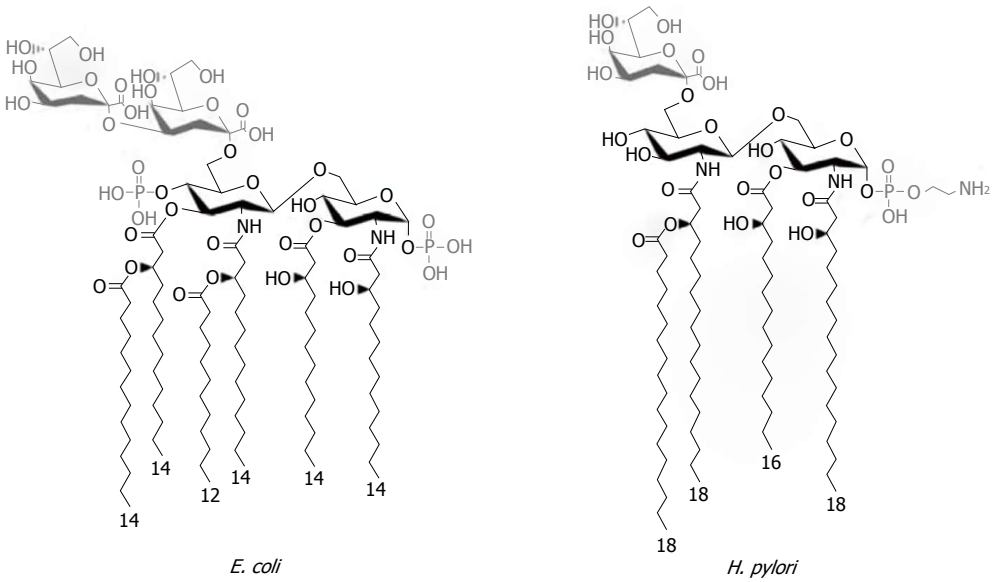

Figure 1 Chemical structures of *Helicobacter pylori* and *Escherichia coli* Kdo-lipid A domains. The majority of *Escherichia coli* (*E. coli*) species express lipid A composed of two *gluco*-configurated hexosamine residues, two phosphate groups at the 1- and 4'- positions, and six C12-C14 long fatty acids. In contrast, the low immunogenic lipid A of *Helicobacter pylori* (*H. pylori*) is a tetraacylated molecule with the long acyl chains C16-C18 that is lacking the 4'-phosphate group. Modified from Cullen *et al*[34].

ylation are necessary for LPS to express its full biological activity[31]. The underphosphorylation and underacylation of *H. pylori* lipid A moieties promote the lipid's low endotoxicity and biological activity[26]. *H. pylori* LPSs, interpreted in the context of their lipid A, possess a significantly lower ability to induce the production of cytokines, nitric oxide, and prostaglandin E_2; show diminished potential to activate natural killer (NK) cells; barely induce the expression of E-selectin; and are unable to impair the activity of suppressor T lymphocytes[38-42]. These suggest that this lipid should be treated not as a typical endotoxin, but rather as a type of matrix that enables *H. pylori* to interact with and modulate the host environment[37].

O side chains of *H. pylori* LPS: The idea of molecular mimicry

Considering the role of *H. pylori* LPS in the course of gastroduodenal infections, several studies have analyzed the relevance of O side-chain repeating units. In contrast to other pathogens, *H. pylori* LPS O antigen is strongly conserved, which suggests that its role in the pathogenesis of *H. pylori* is not related to weak endotoxic activity. The O side chain of *H. pylori* can be fucosylated and thus mimics human Lewis molecules and other related blood-group antigens: Le^X; Le^Y; and, in certain strains, Le^a, Le^b, Le^c, sialyl-Le^X, and H-1 antigens. The side chain can also mimic the antigens of blood groups A and B[29,42,43]. Inactivation of the *H. pylori* Le^X and Le^Y determinants results in the unsuccessful colonization of mice *in vivo*[44-46]. The biosynthesis of *H. pylori* LPS follows a pathway that is different from all established synthesis cascades. The translocation of the O chain is accomplished by Wzk translocase, which is essential for the cell surface expression of Le antigens[47]. During persistent infection, the diversity of *H. pylori* LPS tends to increase[48], especially in relation to poly (C) tracts in the gene encoding α-1,3-fucosyltransferases as well as a poly (C) tract and poly (TAA) repeats in the gene encoding α-1,2-fucosyltransferase[49,50]. The phenomenon of LPS phase variation results in increased heterogeneity of the bacterial population which enables *H. pylori* to more precisely adapt to the changing environment of the gastric mucosa[36,51]. Considering the similarities between Le^X and Le^a or Le^Y and Le^b determinants, it has been suggested that the host Le phenotype may preferentially select for the expression of Le determinants by *H. pylori*[52]. Thus, the host milieu promotes a selection of bacterial strains with particular characteristics that facilitate adaptation and survival in the gastric mucosa of the individual host and shape the bacterial community structure[47]. An investigation of the genetic basis of *H. pylori* Le biosynthesis showed that despite functional similarity, low sequence homology occurs between bacterial and mammalian α-1,3/4- and α-1,2-fucosyltransferases. Thus, the expression of Le antigens in *H. pylori* and these antigens' role in the mimicry phenomenon could be influenced by several factors: the regulation of fucosyltransferase genes, the activity and expression levels of functional enzymes, the preferences of the expressed enzyme for distinctive acceptor molecules, and the availability of activated sugar intermediates[44].

The poorly endotoxic properties of *H. pylori* LPS and the expression of Le^X or Le^Y determinants in *O*-specific chains suggest that antigenic mimicry induced by *H. pylori* LPS may allow the bacterium to avoid the host immune response *via* the induction of potentially autoreactive anti-Le^X or anti-Le^Y antibodies, as well as by strengthening the adhesion process. The functional role of *H. pylori* Lewis antigens in the adhesion of bacteria to the human gastric mucosa has been reevaluated by studying the *in*

situ adhesion of the strains with or without the expression of BabA in patients with various gastric pathologies. It was concluded that BabA is a major *H. pylori* adhesin that mediates *H. pylori* binding to gastric epithelial cells *via* a mucosal Le^b blood-group antigen. In contrast, it was reported that *H. pylori* LPS Le^x determinants play a distinct but minor role in adhesion to the human gastric epithelium[53] and that related strains are not able to colonize C3H/HeJ mice[54]. However, more recent studies showed that the polymeric Le^x structure in the O antigen of *H. pylori* LPS is specifically recognized by β-galactoside-binding lectin (galectin-3), which has been identified as a gastric receptor[55]. Previously, it was shown that the core region of LPS may bind laminin (a molecule of the host ECM) and thus contribute to the colonization process[56].

Key findings

Among *H. pylori* virulence factors, a special role is played by LPS. This molecule's unique structure and low biological activity promote the survival of the bacterium in the gastric mucosa, despite the existence of various immune barriers. Underphosphorylation and underacylation of lipid A result in the low endotoxicity and biological activity of *H. pylori* LPS. Fucosylation of the *H. pylori* O antigen results in the phenomenon of antigenic mimicry, in which bacterial fucose residues imitate human Le blood-group antigens. This imitation allows the bacterium to avoid host immune responses and contributes to prolonged infection.

HOST CELLULAR IMMUNE BARRIERS *VS H. PYLORI* LPS

Pathogens may modulate host immune responses by interfering with host recognition and signal transduction mechanisms[57]. During the co-evolution of *H. pylori* and its host, the bacterium evolved complex strategies to impair immune defenses while maintaining a limited, balanced inflammatory response[58]. Several *H. pylori* compounds reduce the inflammatory response and the recognition of bacterial antigens by the host immune system (Figure 2). The immunomodulatory activities of VacA, CagA, γ-glutamyl transpeptidase, arginase, and several adhesins have been shown[3,58-64]. The release of *H. pylori* LPS into an infectious niche may play an important role in the induction of both local and systemic inflammatory responses. This induction may be a consequence of direct LPS-cell interactions or cell-to-cell cytokine-mediated crosstalk. Changes occurring in the gastric epithelium colonized by *H. pylori* lead to the penetration of bacterial antigens through the basal membrane, where they bind to the ECM and, *via* pathogen recognition receptors (PRRs), interact with immune cells infiltrating the lamina propria and induce the production of cytokines. Moreover, the soluble antigens of *H. pylori* may enter the circulation and induce systemic effects[65,66] (Figure 3).

H. pylori LPS: An atypical PAMP

H. pylori, similarly to many intestinal microorganisms, has developed mechanisms to vary its LPS chemistry to subvert recognition by innate immune receptors[67]. Bacterial LPSs are pathogen-associated molecular patterns (PAMPs), or so-called "alarmins", which allow the recognition of bacterial invasion and trigger the innate immune response of the host[68]. LPSs and other PAMPs, including lipoproteins, peptidoglycan, flagellin, double-stranded RNA, CpG-DNA, and zymosan, are recognized by PRRs on the cells of the first line of immune defense: macrophages and dendritic cells (DCs). Toll-like receptors (TLRs) and nucleotide-binding domain, leucine-rich repeat-containing receptors (NLRs) are well-characterized PRRs that display a high degree of PAMP specificity. In contrast to the adaptive response, innate immunity is not specific. Each type of PRR can differentiate microbial components from similar structures, *i.e.*, patterns or molecular signals, that are unique to host cells, allowing distinction between self and non-self[68,69]. The recognition of PAMPs induces the production of proinflammatory cytokines and the maturation of DCs, which in turn result in the activation of a specific immune response[70,71].

In the context of infections caused by Gram-negative bacteria, LPS constitutes the most dominant and suitable PAMP[72,73]. The structure of lipid A, the expression of Le antigens, and the fucosylation patterns in *H. pylori* LPS may have multiple effects on immune responses. The interactions of lipid A with host cells are mediated by cellular and soluble receptors: (1) serum LPS-binding protein (LBP); (2) the membrane CD14 receptor; (3) sCD14 protein, a soluble form of the CD14 receptor; and (4) TLR4 bound to MD2 molecule, that is used for signaling *via* recruitment of the TIR domain containing MyD88 and TIRAP adaptor proteins or, alternatively, of the TRAM and TRIF proteins, leading to the activation of nuclear factor κB or IRF3/7 transcription factors. This events result in the production of proinflammatory cytokines and type I interferons (IFNs)[73,74]. Studies conducted on two types of cellular systems, 70Z/3 cells expressing CD14 and an epithelial cell lineage with CD14-dependent activation, confirmed that *H. pylori* LPS, although much less active than *E. coli* LPS, stimulates cells to secrete interleukin (IL)-8 *via* CD14[75]. Lower efficiency in LBP binding may be one of the explanations for the low biological activity of *H. pylori* LPS, which is especially observed in the activation of human monocytes. Although *H. pylori* LPS binds LBP less efficiently than does *E. coli* LPS[76], the level of circulating LBP significantly rises in *H. pylori*-infected patients with gastritis and is even more elevated in *H. pylori*-infected patients with coronary heart disease (CHD), most likely as a consequence of the chronic inflammatory response and endothelial dysfunction[77]. Through LBP, LPS is detoxified in the circulation, mainly by its incorporation into low-density lipoproteins (LDLs)[78]. However, considering LPS/LBP/LDL interactions in CHD patients may serve as a mechanism that enables the deposition of *H. pylori* LPS in the vascular endothelium, thus enhancing the TLR4-dependent inflammatory response.

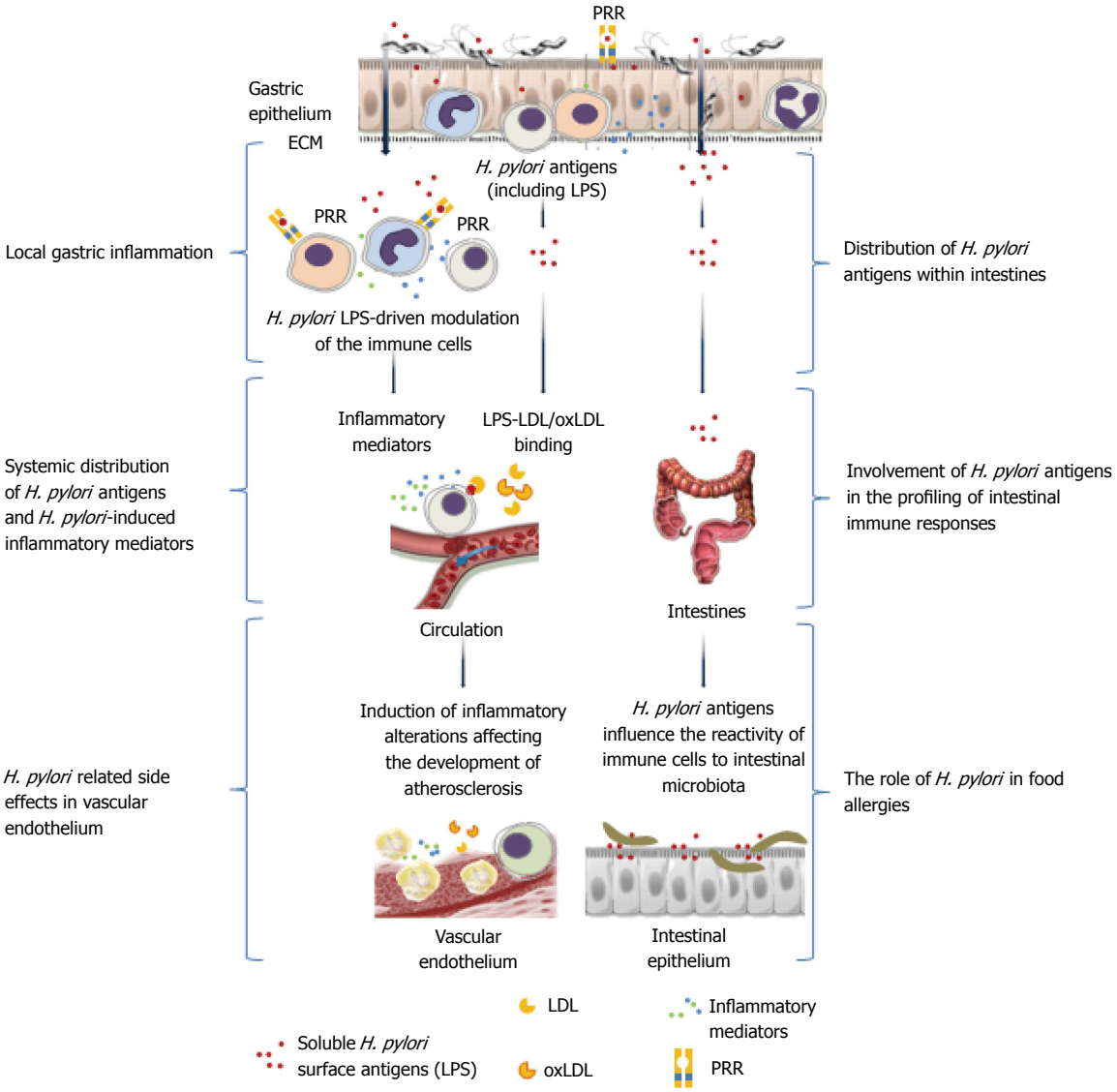

Figure 2 ***Helicobacter pylori*** **lipopolysaccharide-mediated immunomodulation.** The effector functions of both natural and adaptive immune cells could be down-regulated by various lipopolysaccharide (LPS)-dependent mechanisms, making the persistence of *Helicobacter pylori* (*H. pylori*) infection possible. These probable mechanisms might include LPS-dependent escape of phagocytosis due to apoptosis of polymorphonuclear cells, downregulation of the cytotoxic activity of natural killer (NK) cells and expansion of NK cells producing regulatory interleukin (IL)-10, expansion of natural killer T cells, inhibition of antigen presentation by mature macrophages, and downregulation of the lymphocyte proliferation indirectly caused by LPS-driven macrophage arrest. Stimulation of B lymphocytes in response to *H. pylori* LPS may result in the production of anti-Lewis antibodies, which, together with host Lewis antigens, form immune complexes which may induce complement (C)-dependent inflammation. ECM: Extracellular matrix; PRRs: Pathogen recognition receptors; oxLDL: Oxidized low density lipoprotein (LDL).

The variation in bacterial lipid A structures might be a successful strategy for escaping recognition by the innate immune system and blocking TLR4 signaling. *In vitro* studies showed that moieties of lipid A from *H. pylori* LPS are poorly recognized by human TLR4[79]. This phenomenon is due to the presence of fewer but longer (16- to 18-carbon) acyl chains. The potential of these pathogens to cause severe chronic disease in humans is attributed, at least in part, to their relatively low ability to activate TLR4 signaling[67]. However, the advantage of this mechanism for the persistence of *H. pylori* is limited in the gastric milieu because human gastric epithelial cells do not express functional TLR4, which is present on the surface of monocytes and macrophages[80]. *H. pylori* lipid A, which is unable to trigger a signal through TLR4, can act through TLR2, expressed on both epithelial cells and macrophages, which may compensate for a lack of sufficient TLR4 signaling[81]. It has been shown that LPSs from certain *H. pylori* strains can antagonize TLR4. The antagonistic activity of *H. pylori* LPS and its binding to TLR2 might give the bacterium an advantage over the host, and this phenomenon might be associated with the clinical outcome of *H. pylori* infection[79]. It was shown that the presence of *cag* pathogenicity island (PAI) genes may be crucial for the synthesis of bioactive lipid A molecules that stimulate TLR4-mediated expression of mitogen oxidase 1 (Mox1) in gastric pit cells, which could be involved in the initiation of mucosal cell inflammatory and immune responses against *H. pylori* infection[82,83]. However, the genomic and molecular bases for the link-

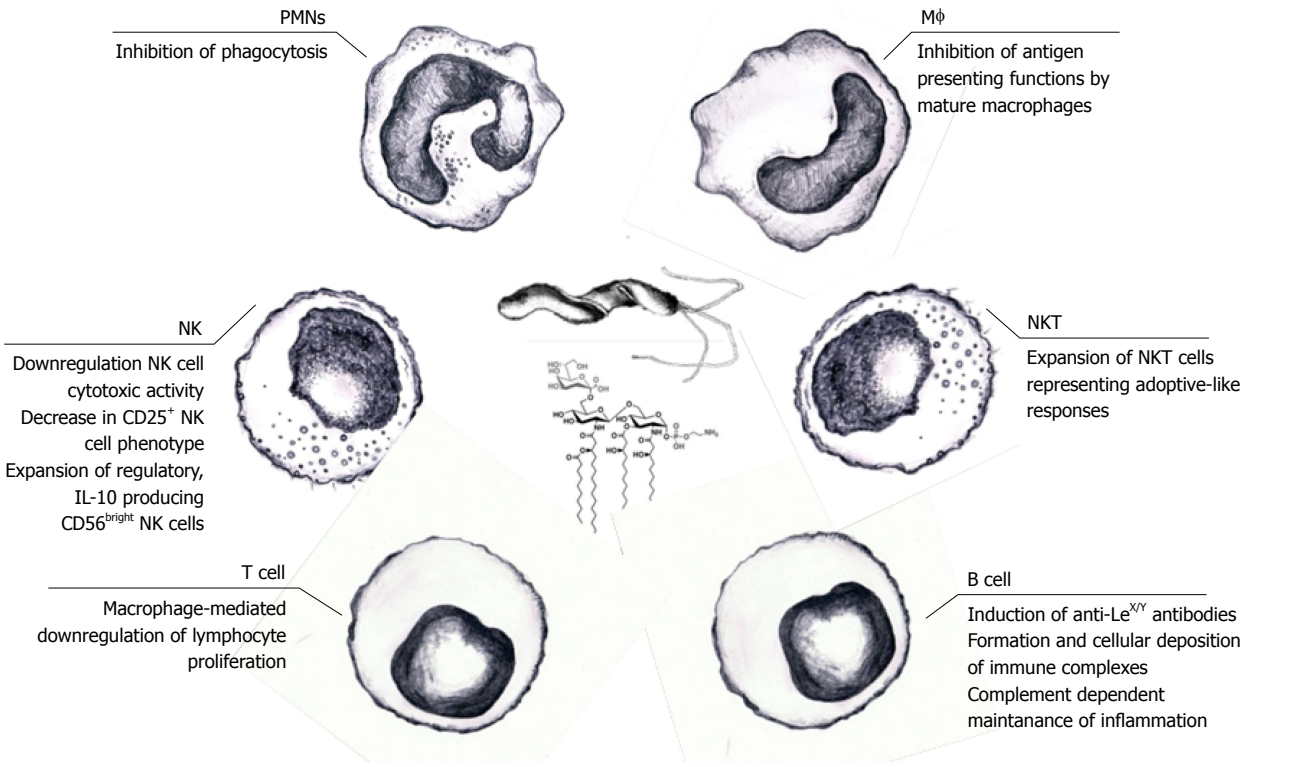

Figure 3 Local and systemic consequences of *Helicobacter pylori*-driven immunomodulation. *Helicobacter pylori* (*H. pylori*) lipopolysaccharide (LPS) may facilitate colonization of the gastric mucosa through extracellular matrix proteins and induction of local inflammation. Increased permeability of the gastric epithelium due to the activity of *H. pylori* proteins such as urease and vacuolating cytotoxin, which contribute to the degradation of intercellular tight junctions, may result in broad interactions of soluble *H. pylori* LPS with host cells. This LPS can bind to various immune cells infiltrating the mucosal basal lamina or even enter the circulation, where the LPS may contribute to the inflammatory response *via* a direct influence on immune cells or through the formation of complexes with low density lipoprotein (LDL)s, and possibly oxidized LDL. Released *H. pylori* LPS can also move along the gastrointestinal tract and, together with the intestinal microbiota, may induce complex immunoregulatory mechanisms. These interactions can result in an increased expression of adhesins, pathogen recognition receptors (PRRs), and proinflammatory cytokines. Different PRRs can mediate the interactions of *H. pylori* LPSs with the immune cells, including Toll-like receptor 4 or 2, dendritic cell-specific intracellular adhesion molecule-3-grabbing non-integrin, and triggering receptor expressed on myeloid cells-like receptors. The signaling pathways triggered by these receptors may cause cytokine secretion. NKT: Natural killer T lymphocytes; PMNs: Polymorphonuclear cells.

age between *cag*PAI genes and the synthesis of bioactive lipid A remain unsolved. Until recently, lipid A was considered the only component of LPS, determining its biological activity. However, since the discovery of Le^X in the LPS of *H. pylori*, several different biological functions have been attributed to the presence of Le antigens. Several proposed functions include enhancement of colonization, escape from host recognition, modulation of the activity of immune cells, and induction of gastric autoimmunity[44].

It has been shown that due to LPS phase variation, *H. pylori* evades binding to surfactant protein D (SP-D) and may persist in the gastric mucosa[44,58]. This phenomenon caused by changes in the fucosylation of the O chain, which is concomitant with slipped-strand mispairing in a poly (C) tract of the fucosyltransferase A (*fut T1*) gene[83]. Recently, two antigenic types of *H. pylori* LPS have been proposed: LPS with a highly antigenic epitope (HA-LPS) and a weakly antigenic epitope (WA-LPS), which is expressed after the removal of a β-*N*-acetyl-*D*-glucosamine residue, a highly antigenic determinant. This antigenic conversion, resulting with the loss or lack of only one β-linked *D*-GlCNAc residue, may serve as an escape mechanism for *H. pylori*, enabling the bacterium to evade the host antibody-mediated immune response. In the presence of SP-D, WA-LPS possesses a stronger ability to upregulate TLR4 expression, proliferation of epithelial cells, inflammation and tumorigenesis[84].

Whether the Le^X and Le^Y determinants are involved in the pathways of cytokine signaling is unclear. It has been shown that *H. pylori* LPSs, with or without Le^{XY} determinants, differ in their ability to induce the production of inflammatory cytokines by peripheral blood mononuclear leukocytes (PBMLs). The lack of Lewis determinants in *H. pylori* LPS results in a significant reduction in its ability to induce TNF-α secretion compared with *H. pylori* LPS containing Le^{XY} antigenic moieties or standard *E. coli* LPS[85]. Little is known about the recognition of bacterial Le determinants by the immune cells of the host. Successful pathogens may manipulate signaling through bacterial structures that modify TLR signaling. For instance, *Mycobacterium tuberculosis*, due to the interaction of mannose-capped lipoarabinomannan (ManLAM) with the mannose receptor, inhibits LPS-induced IL-12 production by macrophages[86]. Additional receptors such as DC-specific intercellular adhesion molecule (ICAM)-3-grabbing non-integrin (DC-SIGN) on DCs, work together with the mannose receptor to inhibit antimicrobial and anti-inflammatory responses by modifying the effects of subsequent TLR activation[87].

It has been shown that whole *H. pylori* bacteria and their LPSs bind to DC-SIGN not only *via* Le carbohydrates but also through galactose moieties[88,89]. It was suggested that differences in *H. pylori* binding affinity for DC-SIGN are determined by the phase variation[90]. The ability of *H. pylori* to bind DC-SIGN might allow the bacterium to modulate the T helper cell 1 (Th1)/T helper cell 2 (Th2) balance and could be crucial for the control of *H. pylori* infections. Activated lymphocytes more effectively control bacterial growth and might diminish inflammation in the gastric mucosa by releasing cytokines, most likely of the Th2 type[90]. Beyond TLRs and DC-SIGN receptors, other molecules, such as triggering receptor expressed on myeloid cells (TREM)-like and nucleotide-binding oligomerization domain 1 (NOD1) receptors, are also engaged in *H. pylori*-driven immune responses[91]. As shown in recent studies, the stimulation of gastric epithelial cells by *H. pylori*-derived NOD1 ligands leads to a production of host defense factors, such as IFN-β, IFN-γ, and IFN-γ-induced protein 10 (IP-10), all of which regulate bacterial growth. The molecular mechanisms of NOD1-mediated mucosal host defense against *H. pylori* are not completely understood but are at least partially dependent on the presence of a functional TIVSS. Interestingly, TLR-dependent proinflammatory cytokine responses are remarkably enhanced in the presence of NOD1 ligands. Thus, synergetic TLR-NOD1 activation in the gastric epithelium should be considered[92].

ESCAPING PHAGOCYTOSIS

Host recognition of microbial invasion induce the recruitment of neutrophils and mononuclear cells into the lamina propria of the gastric mucosa which depends on the density and avidity of adhesion-mediated molecules expressed on leukocytes and endothelial cells. The majority of adhesins, such as ICAM-1 and vascular adhesin molecule-1, are upregulated in the antral mucosa in patients with *H. pylori*-related gastritis. A higher level of E-selectin was shown in the gastric mucosa of individuals infected with *H. pylori* strains positive for the *cag*PAI. These findings indicate that E-selectin and its ligands preferentially mediate the extravasation of mononuclear cells and their migration into inflamed tissues[93]. In this context, a question arises: why are the phagocytes, not able to effectively destroy and eliminate *H. pylori*? It has been shown that several mechanisms allow *H. pylori* to alter phagocyte functions, especially by evading opsonization, actively retarding phagocytosis, affecting membrane trafficking, and inhibiting phagosome maturation[94]. The anti-phagocytic properties of *H. pylori* depend on the presence of the *cag* PAI[95], sialic acid-specific and heparan sulfate-binding proteins[96] and on the expression of various ECM proteins[26]. *H. pylori* LPS may also have various effects on phagocytes. In an *in vitro* study, *H. pylori* LPS diminished the ingestion of *H. pylori* by human peripheral blood polymorphonuclear leukocytes (PMNs)[97]. This anti-phagocytic effect of *H. pylori* LPS was dose dependent and neutralized by recombinant LPS-binding protein (rLBP). LBP is thought to primarily function in facilitating LPS-stimulated cytokine synthesis by monocytes and macrophages. However, LBP also enhances the later stages, affecting bactericidal/permeability-increasing protein (BPI) activity and opsonizing Gram-negative bacteria and thus playing a more direct role in host defense[98]. It is possible that LBP reduces the concentration of BPI required to kill bacteria[99]. The LPS-mediated attachment of *H. pylori* to laminin may affect the effectiveness of the engulfment process[100]. This mechanism may limit the availability of bacteria to phagocytes. Another anti-phagocytic mechanism of *H. pylori* LPS could be associated with LPS-driven apoptotic changes in phagocytes[97]. Previous findings implicated caspase-3 involvement in gastric mucosal inflammatory responses to *H. pylori* LPS and suggested the participation of nitric oxide synthase 2 in the amplification of the cell death signaling cascade[101]. *In vivo, H. pylori* LPS may diminish bacteria elimination and, despite abundant granulocyte infiltration in the gastric mucosa, promote persistence of the infection.

MODULATION OF NK CELL ACTIVITY

There is a growing set of data concerning the interplay of *H. pylori* antigens with NK cells and its consequences in the course of infection. The main function of NK cells, which are large granular lymphocytes representing the innate immune system, is to promote major histocompatibility complex (MHC)-unrestricted killing of both target cells infected by viruses or bacteria and tumor cells[102]. NK cell-dependent responses are especially important in defense against pathogens that induce extensive cell damage, apoptosis, or cancerogenic changes. *H. pylori* bacteria fulfill all of these criteria. The predominance, heterogeneity, and distribution of NK cells at different sites within the gastric mucosa reflect a potential functional role for these cells during *H. pylori* infections[103]. $CD8^{-}CD16^{-}CD56^{+bright}$ NK cells in the gastric mucosa of *H. pylori*-infected subjects have likely adapted to respond to such bacterial infections. NK cells may respond by robust IFN-γ secretion for both direct *H. pylori* stimulation and indirect antigen presenting cell (APC)-dependent cytokine activation[104-106]. Regarding the anti-phagocytic properties of *H. pylori* LPS, it is unclear how this LPS influences NK cell activity compared with the effects of other surface *H. pylori* antigens and standard *E. coli* LPS. It was found that *H. pylori* LPS, but not *E. coli* LPS or *H. pylori* glycine-acid extract (GE) of surface antigens, downregulated the natural cytotoxic activity of peripheral blood lymphocytes, which also correlated with a diminished ability of PBMLs to produce IFN-γ and IL-2 and a retained but very low secretion of IL-10[107]. *H. pylori* LPS-driven downregulation was more intense in *H. pylori*-infected individuals. The activity of *H. pylori* LPS, but not GE or *E. coli* LPS, was related to a decrease in the cytotoxic properties and propagation of NK cells ($CD3^{-}CD56^{+}$). The *H. pylori* LPS-driven downregulation

of lymphocyte cytotoxicity was also accompanied by the expansion of natural killer T (NKT) ($CD3^+CD56^+$) cells exclusively in *H. pylori*-infected donors. This might be explained by the previous *in vivo* stimulation of immune cells with *H. pylori* antigens, including LPS, and the adaptive-like properties of NKT cells[108]. The abundant population of NK cells in *H. pylori*-infected individuals expresses the $CD56^{bright}$ phenotype, exhibiting regulatory rather than cytotoxic activity[109]. Lindgren *et al*[104] suggested that $CD56^{bright}$ NK cells present in the gastric mucosa respond to bacterial infections by cytokine production, which influences the course of innate defense. Thus, the response of NK cells to *H. pylori* most likely depends on the type of antigenic challenge. *H. pylori* antigens may differ in their ability to induce a different cytokine network, which in turn may positively (by GE antigens) or negatively (by LPS) modulate NK cell cytotoxic and secretory activities[107]. The *H. pylori* LPS-mediated decrease in lymphocyte cytotoxicity is accompanied by a lack of $CD3^-CD56^+CD25^+$ NK cell propagation, inhibition of proinflammatory cytokine expression, and intense expansion of IL-10-producing NK cells. These results are particularly interesting in the context of the results obtained for *E. coli* LPS, which was found to stimulate the propagation of human $CD56^+CD3^-$ NK cells, followed by a substantial increase in cytolytic activity and IFN-γ production[110]. This expansion might be driven by monocyte-derived DCs[111]. Using a guinea pig model, it was confirmed that *H. pylori* GE antigens stimulated the cytotoxic activity of lymph node lymphocytes *in vitro*, whereas *H. pylori* LPS did not possess such potential and thus might have promoted the development of chronic infection[112].

T LYMPHOCYTES AND ADAPTIVE IMMUNE RESPONSES

LPSs have various effects, mainly on myeloid cell lineages, including induction of acute phase responses, leukocytosis, moderate fever, infiltration of defense cells into the site of infection, and activation of antimicrobial mechanisms. If not excessive, this response is crucial for the elimination of pathogens. The role of LPS in the development of an antimicrobial humoral response was evaluated in a mouse model where LPS induced the polyclonal activation of B lymphocytes, and secretion of antibodies with different specificities was observed[33,113]. The mechanisms of LPS involvement in adaptive cellular antimicrobial immunity are not yet known. In several studies, LPS has been shown to stimulate human T lymphocytes to proliferate and secrete the Th1-type cytokines IFN-γ, IL-12, and TNF-α. However, T cell activation depends on accessory myeloid cells that provide costimulatory signals[114-116]. Although all of these findings support the hypothesis that LPS could be involved in cellular adaptive antimicrobial immunity, it has been shown that humans may be divided into LPS responders and non-responders[115]. The type of LPS-driven cell response may have implications for the outcomes of infections with Gram-negative bacteria, including *H. pylori*. It has been shown that *H. pylori* LPS itself possesses a very weak, if any, capacity to stimulate the proliferation of PBMLs from *H. pylori*-infected dyspeptic patients[117] or the lymphocytes of guinea pigs with induced *H. pylori* infection[112]. However, in the presence of IL-2, a lymphocyte growth factor, *H. pylori* lysates or LPS can effectively stimulate human lymphocytes. The role of the interaction between IL-2 and the macrophage CD14 surface antigen, serving as the LPS-binding site, in the activation of human monocytes was reported by Bosco *et al*[118]. In another study, it was shown that downregulation of *H. pylori* LPS-driven PBML proliferation was determined by the susceptibility of host cells to bacterial LPS and could have been a result of the direct influence of *H. pylori* LPS on non-adherent lymphocytes or a consequence of an indirect effect of the LPS preparations on monocyte-derived macrophages, known to be the main targets of bacterial LPS[119]. These results revealed that in the milieu of *H. pylori* LPS, but not *E. coli* LPS, only mature macrophages from LPS responders expressed inhibitory activity toward lymphocytes which could result from changes in cytokine production; the expression of surface co-stimulatory molecules; the production of non-protein mediators, such as oxygen free radicals; and changes in TLR4 expression on macrophages[120]. *H. pylori* LPS not only activates phagocytes to release oxygen free radicals but also increased nicotinamide adenine dinucleotide phosphate oxidase and TLR4 expression on gastric epithelial cells leading to elevation of oxidative stress[15]. It has been shown that elimination of regulatory lymphocytes from the population of *H. pylori*-specific memory T cells increased their proliferation in response to *H. pylori* antigens and abolished the effect of anergy[121]. It could be speculated that *H. pylori* LPS affects the macrophage-lymphocyte interactions contributing to prolonged *H. pylori* infection. Immunosuppression induced by *H. pylori* protein components, such as VacA and CagA antigen, has also been suggested to be involved in the chronic nature of *H. pylori* infections[59-64,122].

These bacteria may alter the Th1/Th2 balance to evade the immune response of the host. Th1 polarization of the gastric immune response may be induced by different *H. pylori* components, including LPSs, enhancing IFN-γ and IL-12 secretion and inhibiting IL-2 production and cell proliferation, which may be necessary for Th2 responses[123,124]. It has also been shown that *H. pylori* modulates the Th1/Th2 cell balance through a phase-variable interaction between LPS and DC-SIGN. Lewis-positive *H. pylori* variants were shown to bind DC-SIGN C-type lectin present on gastric DCs, and this interaction blocked Th1 cell development, whereas Lewis-negative *H. pylori* variants that were not involved in binding to DC-SIGN induced a strong Th1 response[90].

A growing number of reports suggest that the Th17 cells identified by their production of IL-17 are involved in *H. pylori* induced inflammation[125]. *H. pylori* colonization and *H. pylori*-induced inflammation were more

intense in wild-type mice than in IL-17-deficient mice, indicating that IL-17 may not contribute to protection, instead playing a role in the development of inflammation[126]. In another study, anti-IL-17 treatment resulted in a reduced *H. pylori* burden and lower inflammation in the stomach, suggesting that IL-17 neutralization contributes to bacterial clearance and prevents inflammatory processes[127]. It has been also shown that *H. pylori* specific tumor infiltrating lymphocytes (TILs) of gastric mucosa produce IL-17[128]. The results obtained in animal models are in line with findings based on real-time PCR and Western blotting analyses of human gastric biopsies, in which the upregulation of IL-17 occurred at both the RNA and the protein levels in *H. pylori*-infected biopsies compared with uninfected biopsies[129,130]. The direct implication of LPS or any other *H. pylori* antigen in IL-17 induction has not been clarified yet. However, regardless of the presence or absence of Th1 or Th17 cells, the results described here support the suggestion that gastritis due to *H. pylori* is the result of complex interactions between at least several different T cell subsets.

Key findings

What distinguishes *H. pylori* from other gastric pathogens is its ability to avoid and modulate host immune mechanisms to maintain balanced inflammation in the mucus layer of the stomach. These mechanisms include the manipulation or downregulation of TLR signaling pathways, SP-D binding, and modulation of the network of cytokines secreted by immune cells. All of these mechanisms are determined by the unique structure of *H. pylori* LPS, and mainly the low acylation of lipid A and phase variation in relation to the O antigen. The diminished elimination of *H. pylori* due to the interference of its LPS in the process of phagocytosis and its negative modulation of NK cell cytotoxic and cytokine activities are also being considered. Although the involvement of *H. pylori* LPS in the mechanisms of adaptive immune responses is not yet known, the *H. pylori* LPS-driven alterations in lymphocyte proliferation and macrophage-lymphocyte interactions may contribute to the lifelong persistence of *H. pylori* infection.

WHAT ABOUT ANTI-*H. PYLORI* LPS ANTIBODIES AND AUTOREACTIVE RESPONSES?

It has been hypothesized that *H. pylori* infections induce antibodies that are potentially autoreactive[131-133]. Half of *H. pylori*-infected individuals are positive for the production of serum autoantibodies potentially crossreacting with gastric parietal cells. The correlation between the eradication of *H. pylori* and a subsequent decrease in serum anti-*H. pylori* IgG levels, resulting in the regression of autoimmune gastritis, seems to confirm this suggestion. Candidates for the antigens responsible for the molecular mimicry that causes autoreactivity include *H. pylori* Hsp60, Le antigens and H^+,K^+-ATPase[131-133]. Opinions on a possible role for antigenic mimicry in the interaction between *H. pylori* Hsp60 and the human gastric mucosa are varied because this antigen was not found to be involved in the autoreactive response observed in individuals infected with *H. pylori*[134]. However, in the sera of *H. pylori*-infected patients, elevated titers of anti-*H. pylori* LPS antibodies have been detected[131]. The epitope specificity of human anti-LPS antibodies has been widely discussed. Although controversial, certain data suggest that long-term *H. pylori* infections could induce autoreactive anti-Lewis antibodies that cross-react with the gastric mucosa, contributing to the development of gastric pathologies[44,132]. However, sera from *H. pylori*-infected patients containing anti-canalicular autoantibodies, despite intense binding to Le^X- or Le^Y-positive *H. pylori* strains, still express antigastric autoreactivity. It cannot be excluded that anti-Le^X and anti-Le^Y antibodies occur naturally under physiological conditions because these antibodies are detected in the majority of *H. pylori*-uninfected individuals. However, the elevated levels of these antibodies have been detected more frequently in the sera of *H. pylori*-infected than uninfected individuals, which suggests that infections with these bacteria may promote specific anti-Le antibody production[135]. Anti-Le^X antibodies, depending on their isotype, may play a different role during *H. pylori* infections. The readiness of the host to respond to Le determinants using IgG, but not IgM, could be a risk factor for *H. pylori*-related pathologies. Anti-Le^X IgM was found to facilitate the phagocytosis of Le^X-positive, but not Le^X-negative, strains, suggesting a protective role. In contrast, increased levels of anti-Le^X and anti-Le^{XY} antibodies of the IgG class, either soluble or bound in immune complexes (ICs), might contribute to the pathogenesis of chronic *H. pylori* infections[136,137]. It is worth mentioning that ICs containing *H. pylori* antigens have been detected in the glomeruli of patients with membranous nephropathy and coexisting *H. pylori* infection[138]. Le-anti-Le ICs are also suspected to play a role in the development or the maintenance of the inflammatory response in *H. pylori*-infected subjects with CHD[75]. It has been shown on a murine model that immunization of animals with *H. pylori* induces anti-Le^{XY} antibodies that cross-react with the gastric epithelium, and particularly with the gastric H^+,K^+-ATPase, the proton pump localized to the parietal cell canaliculi[30]. However, the cross-reactive antibodies are specifically directed toward peptide, and not sugar, epitopes. In another study using a mouse model, it was shown that chronic *H. pylori* infection stimulated the production of antibodies interacting with the parietal cell canaliculi that were coupled with synthetic Le antigens[139]. Recent studies have confirmed that anti-Le antibodies are present in most patients with *H. pylori* infection, including those with gastric cancer. The intensity of the anti-Le response is independent of the host Le phenotype but related to the bacterial Lewis phenotype[140]. The role of anti-Le antibodies during *H. pylori* infections remains unclear. It has been suggested

that *H. pylori* anti-Le^{XY} antibodies are locally produced and rapidly bind to gastric mucosal epitopes. Thus, these antibodies do not appear in serum. In healthy humans, cellular barriers, innate immunity, and an efficient physiological clearance system work together to neutralize gastrointestinal LPS. For instance, nutritional lipids guarantee the maintenance of relatively low systemic levels of LPS[141]. However, evidence of increased permeability of the epithelial and endothelial barriers in the milieu of *H. pylori* products, such as urease and VacA, may suggest the need for a change in the approach to *H. pylori* LPS immunogenicity[66]. In this case, the strong binding of cholesterol by *H. pylori* surface components should also be taken into account[142,143].

Key findings

The role of autoimmune responses in the pathologies associated with *H. pylori* infection must also be taken into consideration. The molecular mimicry involved in autoreactivity might be directly induced by *H. pylori* surface antigens, of which LPS is the most prominent cross-reactive candidate. Gastric pathologies can be induced by anti-Le antibodies that cross-react with Le determinants exposed on the gastric epithelium. Le-anti-Le ICs are also suspected to be associated with the maintenance of *H. pylori*-related inflammatory responses.

CONCLUSION

The data summarized in this review support the suggestion that *H. pylori* LPS evolved during the co-existence of these bacteria with their host, enabling the bacteria to "live in peace". This phenomenon at least partially depends on the immunomodulatory properties of *H. pylori* LPS and its influence on host cell barriers and the condition and responsiveness of immune cells. Many studies have shown that *H. pylori* components may facilitate the colonization process, and especially the immune response of the host, during the course of *H. pylori* infection. This *H. pylori*-driven interaction might result from positive or negative modulation. Among the negative immunomodulators, a prominent position is occupied by a vacuolating toxin and CagA protein. However, in light of the recent studies presented in this review, it is necessary to enrich this panel with *H. pylori* LPS. Together with CagA and VacA, this LPS suppresses the elimination of *H. pylori* bacteria from the gastric mucosa by interfering with the activity of innate and adaptive immune cells. In particular, the LPS diminishes the inflammatory response and affects the adaptive T lymphocyte response, thus facilitating the development of chronic infections. The complex strategy of *H. pylori* bacteria for surviving in the gastric mucosa of the host involves both structural modifications of LPS lipid A to diminish its endotoxic properties and the expression and variation of Lewis determinants, arranged in *O*-specific chains of *H. pylori* LPS. By mimicking host components, this phenomenon leaves these bacteria "invisible" to immune cells. Taken together, these mechanisms allow *H. pylori* to survive and live for many years within their hosts.

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