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TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (6): *Helicobacter pylori*

Immune evasion strategies used by *Helicobacter pylori*

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Abstract

Helicobacter pylori (*H. pylori*) is perhaps the most ubiquitous and successful human pathogen, since it colonizes the stomach of more than half of humankind. Infection with this bacterium is commonly acquired during childhood. Once infected, people carry the bacteria for decades or even for life, if not treated. Persistent infection with this pathogen causes gastritis, peptic ulcer disease and is also strongly associated with the development of gastric cancer. Despite induction of innate and adaptive immune responses in the infected individual, the host is unable to clear the bacteria. One widely accepted hallmark of *H. pylori* is that it successfully and stealthily evades host defense mechanisms. Though the gastric mucosa is well protected against infection, *H. pylori* is able to reside under the mucus, attach to gastric epithelial cells and cause persistent infection by evading immune responses mediated by host. In this review, we discuss how *H. pylori* avoids innate and acquired immune response elements, uses gastric epithelial cells as mediators to manipulate host T cell responses and uses virulence factors to avoid adaptive immune responses by T cells to establish a persistent infection. We also discuss in this review how the genetic diversity of this pathogen helps for its survival.

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Key words: *Helicobacter pylori*; Immune response; Pattern recognition receptors; Phagocytes; T cells; Antigen presenting cells; Gastric epithelial cells; Vacuolating cytotoxin; T4SS

Core tip: *Helicobacter pylori* (*H. pylori*) is an important human pathogen that causes chronic infection in almost half of the population in the world. In the course of 30000 years of co-existence with humans, *H. pylori* has evolved extensive adaptations that allow it to successfully cause persistent infection in its host in the face of a vigorous innate and adaptive immune response. In this review, we discuss innate and adaptive immune responses to *H. pylori* and the mechanisms by which *H. pylori* evades immune-mediated clearance.

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INTRODUCTION

Helicobacter pylori (*H. pylori*) is the main cause of chronic gastritis, gastroduodenal ulcers and gastric cancer[1]. Interestingly, *H. pylori* is responsible for about 90% of cases of peptic ulcer formation[2,3]. The World Health Organization classified *H. pylori* as a class I carcinogen because of the epidemiological link of *H. pylori* infection with a higher risk of development of gastric malignancy[4].

H. pylori infection is typically acquired during childhood and usually becomes a lifelong infection, if left untreated[1]. During *H. pylori* infection the host mounts an immune response, but this response fails to clear the infection and *H. pylori* successfully establishes a persistent infection leading to chronic inflammation. Multiple lines of evidence suggest that the immune response during *H. pylori* infection plays an important role in pathogenesis. *H. pylori* successfully establish a chronic infection by achieving a delicate balance between inducing immune responses and surviving in the inflammatory milieu by using an array of important virulence factors. In this review, we discuss innate and adaptive immune responses to *H. pylori* and the mechanisms by which *H. pylori* evades immune-mediated clearance.

INHIBITION OF INNATE IMMUNE RECOGNITION

Evasion of recognition by pattern recognition receptors

H. pylori evades the innate immune system by a variety of mechanisms. One of these mechanisms is avoidance of detection by pattern recognition receptors (PRR), which are proteins that recognize pathogen-associated molecular patterns (PAMP's). PAMP's include a large group of molecules that are part of microbes and can vary from microbial surface molecules to nucleic acids. When PRR' s recognize PAMP's they induce several extracellular activation cascades such as the complement pathways and various intracellular signaling pathways, leading to inflammatory responses that are essential for clearance of pathogens[5].

H. pylori eludes identification by PRR's by multiple methods, including: avoidance of recognition by Toll-like receptors (TLR's) and inhibition of c type lectin (DC-SIGN) mediated signaling. To avoid recognition by TLR's the bacterium modulates its surface molecules (including LPS and flagellin). Lipopolysaccharide (LPS) is a glycolipid found on the outer membrane of gram negative bacteria[6]. It has three distinct units: lipid A, which is responsible for the toxic effects; a core polysaccharide of five sugars linked through ketodeoxyoctulonate to lipid A; and the O-antigen, an outer polysaccharide consisting of up to 25 repeating units of three to five sugars[7]. *H. pylori* expresses O-antigens with great diversity; the bacterium has Lewis antigens, which are made of carbohydrates, that resemble human blood group antigens[8]. By exploiting this form of molecular mimicry, the bacterium is able to evade TLR's because the normally detectable O-antigen is recognized as a "self" molecule by this type of PRR. In addition to having variable O-antigens, the bacterium also modifies the lipid A portion of the LPS molecule. Modification of this unit is achieved through several pathways, resulting in alteration of the net charge of the microbial surface. This leads to an inability of cationic antimicrobial peptides (CAMP's) to bind to typically negatively charged structures like lipid A[6]. Lipid A, within LPS, is recognized by the human Toll-like receptor 4-myeloid differentiation factor 2 (hTLR4-MD2) complex. *H. pylori* expresses a modified Kdo (3-deoxy-*D*-manno-octulosonic acid)-lipid A structure tetra-acylated with a phosphoethanolamine added at the 1 position of the dissacharide[9], which might promote high resistance to CAMP and decreased activation of the hTLR4-MD2 complex[9]. Cullen *et al*[6] found that the 1 and 4'-phosphatases involved in lipid A synthesis in *H. pylori* act synergistically to produce a bacterial surface that is highly resistant to CAMP attack. In addition, dephosphorylation of *H. pylori* lipid A at the 1 and/or 4' position results in LPS with attenuated hTLR4-MD2 activation. Moran[10] proposed that reduced immunogenicity of *H. pylori* LPS could be due to uncommon phosphorylation and acylation of *H. pylori* lipid A. *H. pylori* LPS binds poorly and at a slower rate to LPS-binding proteins, which are acute phase reactants that aid in LPS binding to CD14 and TLR4 on monocytes/macrophages. This reduced binding of LPS to its receptors results in decreased activation of monocyte-macrophages, preventing their contribution to innate immune response. Interestingly, *H. pylori* LPS has also been shown to possess anti-phagocytic properties *in vitro*[11].

Flagellin is the protein component of bacterial flagella needed for motility and colonization[12]. *H. pylori* rely on five or six polar flagella made of two separate subunits, FlaA and FlaB, to enable movement within the gastric mucus and to counteract peristalsis[13]. TLR5 is a PRR that recognizes flagellin. However, studies showed that *H. pylori* flagellin was not recognized by TLR5, and thus failed to induce nuclear factor (NF)-κB activation[14]. The study also reported that an 8 amino acid stretch in the N-terminal D1 domain of flagellin differed from that of flagellin from bacteria that activated TLR5. One study showed that flagellin, especially FlaA, is not "shed" by the bacteria and thus could not be detected by western blots in supernatants of infected gastric epithelial cells[13]. There were no evident traces of flagellin, which diminished the probability of it interacting with TLR5, allowing for evasion of this mechanism of bacterial recognition. Most flagellated bacteria are able to induce a proinflammatory state by promoting production of IL-8, but *H. pylori* flagellin seems unable to induce IL-8 production in GECs[13].

H. pylori LPS is important not only for the activation

of TLR4 but also because the bacterium expresses Lewis (Le) blood group antigens in the O-antigen portion of the LPS molecule. As mentioned above, this polysaccharide area of the molecule is a clear method of evasion of the innate immune response because the Le group antigen system is biochemically related to carbohydrates present in ABO blood groups. The bacterium employs molecular mimicry to evade recognition by the innate immune system. The group of Le antigens is divided into type 1 (Le^a and Le^b) and type 2 antigens (Le^x and Le^y). Approximately, 80%-90% of *H. pylori* strains express Le^x and/or Le^y antigens, whereas gastric epithelial cells (GECs) also express $Le^{x/y}$ antigens[10,15]. *H. pylori* uses phase variation in the synthesis of LPS, including Le antigens. Phase variation in this context refers to a high frequency of LPS phenotype changes, like a reversible on-and-off switch, that results in loss/gain of certain LPS epitopes, as well as a heterogeneous population of LPS.

It has been suggested that although *H. pylori* LPS is not a strong activator of TLR4, it may be modulating the immune response *via* interactions with DC-specific ICAM3-grabbing non-integrin (DC-SIGN). DC-SIGN belongs to a subset of PRR's termed C-type lectin receptors (CLR's), which are involved in inducing specific genes within cells in response to pathogens as well as in modulating TLR signaling[16]. When CLR's are expressed on dendritic cells (DCs) they detect carbohydrates like mannose, fucose, and glucan, which are common on bacterial surfaces. Ligand binding to these receptors initiates signaling pathways which induce phosphorylation of a subunit of the NF-κB complex and result in an increased rate of transcription of proinflammatory cytokine and chemokine mRNAs, such as IL-8[16]. DCs possessing these receptors are found on all mucosal surfaces as well as in lymphoid organs. Miszczyk *et al*[17] showed that *H. pylori* LPS was able to bind to recombinant human DC-SIGN *in vitro* and that this binding was abolished in the presence of monoclonal antibodies against the Le antigens and when fucose was added. By binding to this receptor it may be possible that the presence or absence of certain carbohydrates at the O-antigen end of the molecule could determine how DCs help T cells mature. Another independent study showed that Le^+ variants from clinical isolates were able to bind to DC-SIGN and have effects on the polarization of the T cell response (Th1 *vs* Th2)[18]. It seems that *H. pylori* targets DC-SIGN to block a polarized Th1 response by phase-variable expression of Le antigens. In addition, this study provided evidence that *H. pylori* strains without Le^x and Le^y were able to evade recognition by DC-SIGN and possibly evade detection by any other mechanism[18].

Inhibition of phagocytic killing

H. pylori infection activates an inflammatory response in its host which leads to the recruitment of macrophages, neutrophils, and lymphocytes to the gastric tissue[19]. *H. pylori* can efficiently inhibit its own uptake by these professional phagocytes. This antiphagocytic phenotype depends on type Ⅳ secretion components encoded by the cytotoxin-associated gene pathogenicity island (*cag* PAI)[20,21]. Macrophages can engulf *H. pylori,* but *the bacterium* has developed mechanisms to avoid killing upon phagocytosis[22-24]. In a study where ingestion of *H. pylori* by human and murine macrophages was monitored using immunofluorescence and electron microscopy, *H. pylori* type I strains (*cag* PAI^+ and vaculating toxin A^+, $VacA^+$) were shown to employ an unusual mechanism to avoid phagocytic killing. Once inside the macrophage, *H. pylori* actively delayed actin polymerization and phagosome formation. *H. pylori*-containing phagosomes then underwent extensive clustering and fusion resulting in the formation of "megasomes" containing multiple bacteria, which caused resistance to intracellular killing[22,25]. Studies also showed enhanced survival of *H. pylori* type I strains in macrophages compared to type Ⅱ strains, which lack *cag* PAI and VacA. *H. pylori* type I strains were shown to reside in compartments with early endosome properties and did not fuse with lysosomes. The study also showed that retention of TACO, a tryptophan aspartate-containing coat protein on phagosomes, inhibited fusion of phagosomes and lysosomes in macrophages infected with *H. pylori* type I strains. It is worth noting that VacA alone plays a significant role in the interruption of the phagosome maturation[24]. By interfering with the phagosome function, VacA might prevent phagocytic killing of *H. pylori*. In fact, a study showed that, by interfering with endosomal traffic, VacA altered the presentation of antigens by B cells[26]. This mechanism would be expected to result in impaired adaptive responses as presentation of antigens to T cells is critical for the initiation of protective immune responses, as will be described in detail below. A related recent study provided evidence that the effects of VacA on endosomal traffic may prevent the development of a strong Th1 response. The study showed that *H. pylori* VacA could redirect the endocytic pathway of the probiotic bacterium *Lactobacillus acidophilus*, which induces a polarized Th1 response, and does this by blocking the induction of key innate cytokines such as IFN-β and IL-12[27]. Like other pathogenic bacteria, *H. pylori* also regulate host trafficking pathways by the selective modification of GTPases in macrophages during infection. *H. pylori* has been shown to disrupt the actin cytoskeleton by suppressing *Rgs1/2*, *Fgd2*, and *Dock8* which are the key regulators of the Rho, Rac, and Cdc42 GTPases, respectively[27]. These are required for the organization and dynamics of actin cytoskeleton needed for proper cell function. This is another mechanism that disrupts phagocyte function and helps *H. pylori* survival in its host[27].

Inhibition of killing by reactive oxygen species and nitric oxide

A major proinflammatory factor produced by *H. pylori* is neutrophil-activating protein (NAP)[28]. *H. pylori*-NAP (HP-NAP) is a 150 kDa oligomeric protein, which increases adhesion of PMNs to endothelial cells, stimulates phagocyte chemotaxis, and activates NADPH oxidase to produce

reactive oxygen species (ROS)[29,30]. However, *H. pylori* produces catalase and superoxide dismutase to detoxify ROS[31,32]. *H. pylori* can also down-regulate CXCR1 and CXCR2 expression in human neutrophils, which act as receptors for the neutrophil recruiting chemokine, IL8; thus, resulting in an inhibitory effect on neutrophil migration and reduced bacterial killing[33]. *H. pylori* also disrupt NADPH oxidase targeting, which was shown to result in the release of superoxide anions in the cytoplasmic membrane instead of the accumulation inside *H. pylori* phagosomes[34].

One antimicrobial host defense mechanism is the generation of NO through the enzyme inducible NO synthase (iNOS). *H. pylori* activates the inducible iNOS in macrophages[35]. A mechanism employed by *H. pylori* to activate iNOS involves urease, an important virulence factor of *H. pylori*. Despite the presence of iNOS *H. pylori* infection persists, which suggests that the iNOS production may be at suboptimal level. *H. pylori* arginase was shown to be an important factor that affords protection of the bacteria against NO mediated killing since macrophages infected with *H. pylori* produce significantly less NO than arginase isogenic mutants[36]. A recent study showed that induction of macrophage arginase Ⅱ (Arg2) restricts iNOS protein expression, elicits apoptosis of macrophages as well as proinflammatory cytokine production, and limits bacterial killing[37], suggesting another mechanism this bacteria uses to escape macrophage-mediated killing. Interestingly, the authors of that study used a chronic infection mouse model to show that $Arg2^{-/-}$ mice infected with *H. pylori* had reduced bacterial colonization and increased gastritis compared with similarly infected wild type mice. $Arg2^{-/-}$ mice infected with *H. pylori* had more $iNOS^{+}$ macrophages in the gastric mucosa expressing higher levels of iNOS and more robust cytokine responses, which led to the suggestion that *H. pylori* induction of Arg2 is part of the bacterial armamentarium to escape host innate immunity together with other mechanisms that target adaptive immunity[37].

MODULATION OF APC FUNCTIONS IN ADAPTIVE IMMUNITY

H. pylori have evolved an array of mechanisms to actively dodge adaptive immunity by interfering with antigen presentation and modulation of T cell responses. Antigen presenting cells (APC), represented by macrophages, DCs and B cells, internalize antigen by phagocytosis or endocytosis, process the antigens and present them to $CD4^{+}$ T cells *via* class Ⅱ MHC molecules. This leads to the initiation of antigen specific T cell response. The gastric mucosa of *H. pylori* infected people has an increase in activated macrophages and DCs. Activated macrophages produce IL-6, IL-1β, IL-12 and tumor necrosis factor (TNF)-α which cause inflammation and help initiate Th1 type responses. In spite of the presence of these effector cells, *H. pylori* successfully establish a persistent infection, suggesting that these effector cells are unable to clear the pathogen. *H. pylori* has also been shown to cause the polarization of APCs. For instance, during atrophic gastritis macrophages are polarized to M1 subtype[38]. *H. pylori* can even control the functions of these APCs differently. A study showed that *H. pylori* mediated activation of DCs and M1 macrophage leads to induction of T cell proliferation and decreased phagocytosis. On the other hand, upon *H. pylori* infection the M2 macrophages produced less pro-inflammatory cytokines and increased anti-inflammatory cytokines compared to M1 macrophages[39]. As alluded to earlier, several studies show that *H. pylori* uses mechanisms to avoid killing by APC and those will be discussed in detail below.

Apoptosis of macrophages

H. pylori causes apoptosis of macrophages using several mechanisms. Inside a macrophage, *H. pylori* activate the ERK1/2 pathway leading to formation of the activation protein (AP-1) complex. AP-1 complex induced c-Myc gene expression and nuclear translocation leading to increased ornithine decarboxylase (ODC) expression and apoptosis of macrophages[40-42]. Another recent study showed an important role for an unknown gene, HP986, which is associated with peptic ulcer and gastric carcinoma in apoptosis of macrophages through a Fas mediated pathway[40]. *H. pylori* VacA protein also causes apoptosis of monocytes. The underlying mechanism of this process involves the amino-terminal 476 residue fragment (p52) of VacA, which activates the NFκB pathway and induces proinflammatory cytokine production, *e.g.,* TNF-α, IL-1β, and induction of NO, ROS and subsequently causes apoptosis of monocytes[43].

Inhibition of DC maturation and function

DCs are important APCs in initiating T cell responses, particularly to mucosal pathogens. *H. pylori* control maturation of DCs and, consequently, limit their ability to present antigens. Transcription factor E2F1, is an important regulator of DC maturation. Using LPS as a stimulator, it was shown that E2F1 expression is downregulated during DC maturation. However, *H. pylori* VacA was shown to inhibit DC maturation *via* restoration of E2F1 since transfection of murine DCs with E2F1 siRNA showed recovery of the inhibited maturation of DCs caused by *H. pylori* VacA[44]. VacA caused reduced expression of surface costimulatory molecules, *e.g.*, CD40, CD80, CD86, MHC class Ⅱ molecule and decreased secretion of IL-1β, IL-12p70 and TNF-α by DCs[44]. Reduced expression of costimulatory molecules could, in turn, dampen effector T cell activation or promote tolerance. In addition to VacA, *H. pylori* CagA also plays a key role in regulating DCs and in inhibiting $CD4^{+}$ T cells' differentiation towards Th1 type cells. Once inside the APC, CagA protein was shown to be phosphorylated leading to the activation of SHP-2. Activated SHP-2 was shown to suppress the enzymatic activation of TBK-1, IRF-3 phosphorylation and nuclear translocation, which caused reduced interferon production by DC[45]. Long term infection with *H. pylori* $cagA^{+}$ strains caused increased

expression of the T cell co-inhibitory molecule B7-H1 (also known as PDL-1) as well as increased IL-10 and IL-23 production by DC. The simultaneous inhibition of DC maturation and IL-12 secretion led to suboptimal Th1 development and activation[46]. *H. pylori* were shown to multiply in DC and impair their function by inhibiting the production of the proinflammatory cytokine IL-12 and increasing IL-10 production[47]. A separate study showed that *H. pylori*-mediated inhibition of DC maturation is independent of the presence of *cag* PAI, but direct contact with the bacteria was required for this inhibitory mechanism[48]. When expression of different co-stimulatory molecules was evaluated after treating DCs with TLR ligands and subsequent infection with *H. pylori* it was found that *H. pylori* inhibit TLR ligand induced DC maturation by inhibiting CD80, CD86, CD40 expression, IL-12, IL-6 secretion and increased production of the anti-inflammatory cytokine IL-10[48]. These studies showed that inhibition of DCs is another mechanism used by *H. pylori* to deter its clearance by the host immune system.

Inhibition of antigen presentation

The proliferation of human $CD4^+$ T cells is triggered by recognition of antigenic epitopes bound to MHC class Ⅱ molecules exposed on the surface of APCs. Antigen presentation by APCs plays an essential role in the initiation of adaptive immune responses. As another approach to inhibit APC function, *H. pylori* use several mechanisms to interrupt antigen presentation, some of which were mentioned above. *H. pylori* inhibits antigen processing by APC by interfering with late endocytic membrane trafficking. *H. pylori* VacA interferes with proteolytic processing of antigens and the generation of T cell epitopes loaded on newly synthesized MHC class Ⅱ molecules (the Ii-dependent pathway of antigen presentation), but it does not affect generation and presentation of epitopes by mature class Ⅱ molecules that recycle from the cell surface (Ii-independent pathway)[26]. Also, possibly linked directly to this, *H. pylori* can also cause impaired antigen presentation by DC by inhibiting export of MHC-class Ⅱ molecules to the cell surface[47]. This observation is directly related to the inability of these DCs exposed to *H. pylori* VacA to degrade Ii (aka, CD74), which requires the action of cathepsins activated by acidic pH[49-51].

Apoptosis of gastric epithelial cells

GEC may act as non-professional APCs, as they express all the elements associated with conventional APCs, including class Ⅱ MHC, CD74, cathepsins and costimulatory molecules[52,53]. Their importance in *H. pylori* infection is obvious as they are the first cell types that come in direct contact with the bacteria and are strategically situated to interact with *H. pylori* and its antigens as well as with lamina propria lymphocytes. In fact, GEC separate the lamina propria immune cells from direct contact with *H. pylori* in the lumen. One of the multiple ways *H. pylori* has been shown to induce apoptosis of GEC is by upregulation of Fas receptor leading to increased interaction with Fas ligand and increased apoptosis[54]. This interaction has also been shown to induce production of ROS[55]. Another mechanism that our group showed previously is *via* the engagement of MHC class Ⅱ molecules on GEC by *H. pylori*, which use urease on its surface as an adhesin and bind to and crosslink MHC class Ⅱ molecules to induce apoptosis in GEC[56]. In yet another mechanism of induction of GEC apoptosis, VacA was shown to induce apoptosis *via* disruption of mitochondrial membranes[57,58].

Using GEC as orchestrators of T cell responses

Activation of T cells requires two signals triggered by (1) recognition by T cell receptor (TcR) of peptides/MHC complexes; and (2) a costimulation by special receptor molecules on APCs. Recognition of antigen by T cells in the absence of the second signal renders T cells unresponsive or anergic. The B7 family of costimulatory/co-inhibitory receptors provides this second signal to initiate responses and some members of this family of receptors serve to regulate or attenuate responses. In addition to their role as on/off switches for T cell activity, recent studies from multiple groups also suggest their role in influencing T cell differentiation and phenotype[59-61]. Our group showed that *H. pylori* can subvert GECs and use them as mediators to inhibit T cell proliferation and cause T_{reg} cell induction from naïve T cells by inducing increased expression of the T cell co-inhibitory molecule B7-H1 on GEC[62,63]. Interaction of B7-H1 with programmed death-1 (PD-1) receptor is also known to cause downregulation of T cell activation and promote the induction of T regulatory cells (T_{reg}) as we have previously shown[62,63]. Because of their suppressive effect on T effector cells, T_{reg} cells may assist in the chronicity of infection (Figure 1). *H. pylori*-mediated B7-H1 upregulation also contributes to apoptosis of effector T cells by engaging PD-1 on their surface[64]. Recently, our group uncovered another mechanism by which *H. pylori* uses its *cagPAI* encoded type 4 secretion system, T4SS, translocated effector protein CagA to downregulate B7-H2 (ICOS-L), which is the only positive T cell costimulatory molecule known among the newer members of this family of receptors. Downregulation of B7-H2 caused decreased Th17 cell response, which correlated with increased bacterial load in the stomach of *H. pylori*-infected mice[65]. As Th17 cells play a very important role in immune protection against extracellular bacteria, *H. pylori* hinders Th17-mediated clearance by preventing B7-H2 expression on the surface of GECs to establish chronic infection (Figure 2).

INHIBITION OF EFFECTIVE T CELL RESPONSE

T helper $CD4^+$ cells (Th) are major effector cells in the immune response to *H. pylori*. The response was initially characterized as a Th1 polarized response[66,67] but more recently other $CD4^+$ T cell subsets have been found in *H. pylori*-infected patients, and those include T_{reg} and Th17

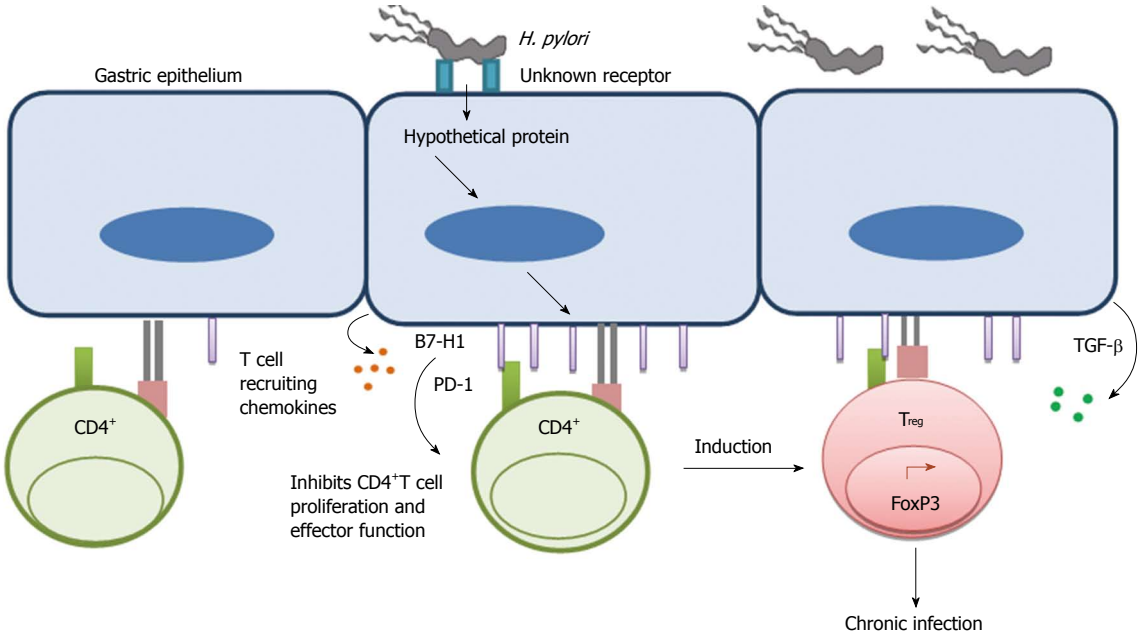

Figure 1 ***Helicobacter pylori*** **uses gastric epithelial cells as a mediator to inhibit T cell function.** Upon binding to an unknown receptor on GEC *Helicobacter pylori* translocate a hypothetical protein, which causes induction of B7-H1 on GEC. Induction of T cell co-inhibitory molecule B7-H1 further inhibits $CD4^+$ T cell proliferation and effector function. It also facilitates induction of T_{reg} cells from naïve $CD4^+$ T cells. This mechanism helps to establish a chronic infection.

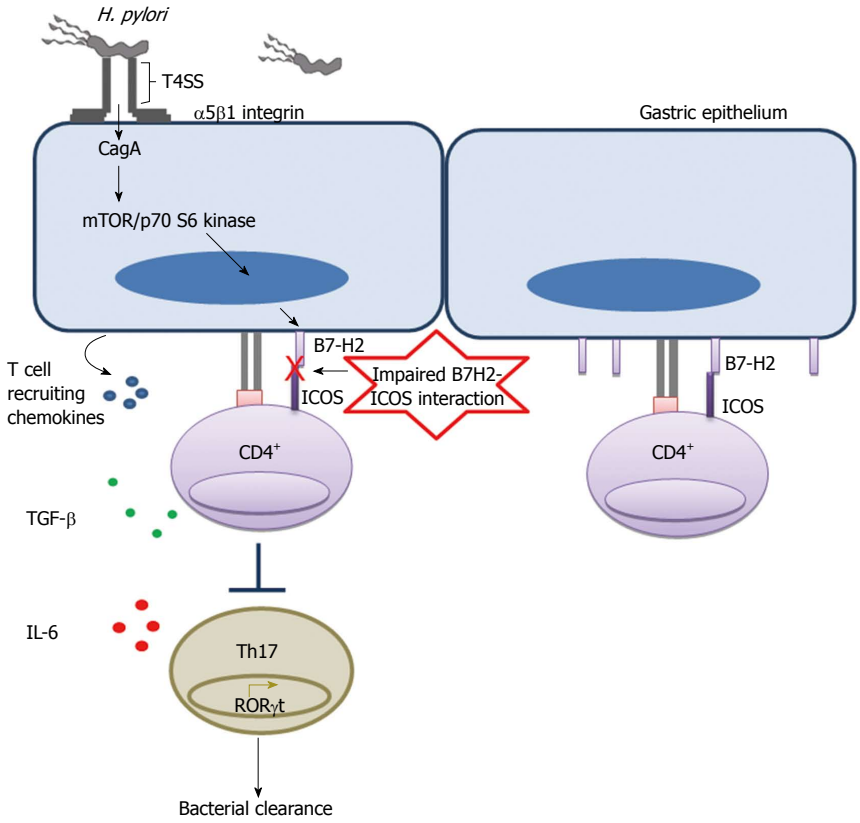

Figure 2 ***Helicobacter pylori*** **mediated downregulation of B7-H2 on gastric epithelial cell inhibits Th17 cell development and facilitates bacterial persistence.** *Helicobacter pylori* T4SS interacts with host receptor integrin α5β1 and translocate effector protein CagA. CagA activates mTOR/p70 S6 kinase pathway and downregulates T cell co-stimulatory molecule B7-H2 expression on GEC. Decreased B7-H2/ICOS signaling further inhibits Th17 cell development from naïve $CD4^+$ T cells and Th17 cell mediated bacterial clearance.

cells[68-71]. The neutrophil-activating protein of *H. pylori* (HP-NAP) was shown to increase IL-12 and IL-23 production by neutrophils and monocytes, which promote Th1 responses. Addition of HP-NAP to antigen-induced T cell lines caused a shift from a predominant Th2 to a Th1 phenotype of specific T cells. HP-NAP also elicited an antigen-specific Th1-polarized T cell response in the gastric mucosa of *H. pylori*-infected patients[72]. Increased production of gamma interferon (IFN-γ) by Th1 cells was shown to cause chronic gastric inflammation[66,73]. On the other hand increased T_{reg} cells produced during *H. pylori* infection suppress mucosal effector T cell responses, which contribute to bacterial persistence, and are also a probable cause of gastric tumor progression[68]. Th17 cells, which produce IL-17A, appear to be crucial in the clearance of extracellular bacteria such as *H. pylori*[74]. IL-17 also acts on GEC to release IL-8, a chemokine that recruits neutrophils, and thus promote gastric inflammation. On the other hand, this IL-17-initiated recruitment of neutrophils is critical for the clearance of the bacteria[75]. A hallmark of *H. pylori* infection is that effector T cell responses are generally impaired during *H. pylori* infection, and T cells from *H. pylori*-infected individuals are hyporesponsive[76]. As this is an important issue in vaccine design efforts, there has been significant effort to address mechanisms that impair T cell responsiveness. *H. pylori* virulence factors that have been reported to play a role in interfering with T cell responses are VacA, γ-glutamyltranspeptidase (GGT), and arginase[77-82]. Recently our group showed *H. pylori* CagA also plays important role in modulating Th17 cell response indirectly by modulating expression of B7-H2 on GEC[65].

Inhibition of T cell proliferation and signaling

As described earlier, the vacuolating cytotoxin, VacA, induces cellular vacuolation in epithelial cells. *H. pylori* disrupt tight junctions between GECs and VacA secreted by *H. pylori* can reach the lamina propria. Once in the lamina propria, VacA can interact directly with T cells. *H. pylori* exploit the recycling of the heterodimeric transmembrane receptor lymphocyte function-associated antigen 1 (LFA-1) by cells for VacA uptake[73]. VacA enters activated primary human T lymphocytes by binding to the β2 (CD18) integrin subunit of LFA-1[83]. Once VacA is inside the cytoplasm of T cells it inhibits their proliferation and activation using several mechanisms. One approach is by interrupting IL-2 signaling, which is required for lymphocyte activation and proliferation. *H. pylori* VacA induces cell cycle arrest[84]. VacA also blocks IL-2 at the transcription level by inhibiting nuclear translocation of nuclear factor of activated T cells (NFAT), an essential transcription factor required for IL-2 promoter activation[84]. Further study into the mechanism of action of VacA on T cell impairment showed that VacA requires its intact N-terminal hydrophobic domain for membrane channel formation and inhibition of T cell proliferation[80]. Furthermore, VacA may reduce the mitochondrial membrane potential of $CD4^+$ T cells to inhibit their proliferation[81]. In addition to preventing calcium influx from the extracellular milieu by formation of anion-specific channels and inhibiting NFAT translocation, VacA also uses a channel independent mechanism to activate intracellular signaling *via* mitogen-activated protein kinases MKK3/6 and p38 as well as the Rac-specific nucleotide exchange factor, Vav, which results in actin rearrangement and defect in T cell activation[77]. VacA mediated apoptosis in T cells is another possible mechanism of immune evasion. There are two pathways of apoptosis initiation. One pathway depends on death receptor and is called the extrinsic pathway; the second pathway depends on mitochondrial activation and is known as the intrinsic pathway. *H. pylori* mediated apoptosis of T cells is independent of death receptor. A mitochondrial pathway was shown to play a critical role in *H. pylori* induced apoptosis since higher expression of antiapoptotic protein Bcl-2 in T cells showed reduced apoptosis by *H. pylori*. Bcl-2 inhibits apoptosis by stabilizing the mitochondrial membrane[78].

GGT is another secreted protein of *H. pylori* which mediates the extracellular cleavage of glutathione, leading to ROS production and induction of a cell cycle arrest in lymphocytes. A study showed that *H. pylori* uses GGT to inhibit T cell proliferation since site directed mutagenesis of GGT in different *H. pylori* strains and inhibition of GGT by acivicin abrogated the inhibitory effect, while recombinant expression of GGT showed inhibition of T cell proliferation. GGT was found to inhibit T cell proliferation by inducing G1 cell cycle arrest through disruption of Ras signaling pathway[79].

Though most studies have shown involvement of VacA and GGT in T cell inhibition, other reports also showed involvement of *cag* PAI in T cell apoptosis. *H. pylori cag* PAI causes apoptosis in T cells in a Fas-dependent manner concurrently with induction of Fas ligand (FasL) in T cells leading to apoptosis[82]. Another virulence factor that impairs T cell function during *H. pylori* infection is arginase, which is important for urea production. Arginase hydrolyzed L-arginine to urea and ornithine. L-arginine is also required for T cell activation and function. Co-culturing of *H. pylori* wild type and arginase mutant bacteria with T cells revealed that arginase caused a significant decrease in T cell proliferation and reduced expression of the chief signal transduction protein CD3ζ-chain of the TCR by decreasing L-arginine availability[85]. Decreased expression of CD3ζ-chain partially explains T cell anergy status in the host, which is a hallmark of *H. pylori* infection.

H. pylori mediated skewing of T cell response towards T_{reg} cells

$CD4^+CD25^{high}$ T_{reg} cells can inhibit infection-induced immunopathology, but may also allow for an increase in the bacterial load and facilitate chronicity of the infection by suppressing protective immune responses[86]. T_{reg} cells are found in increased amounts in the gastric tissue of *H. pylori* infected patients compared to healthy controls[86,87].

Several studies have shown the immunosuppressive roles of T_{reg} cells during *H. pylori* infection[63,86]. Induction of T_{reg} cells appears to depend on the age of the host when they get the infection, since *H. pylori* infected children have increased levels of FoxP3-expressing T_{reg} cells and reduced gastric pathology compared to adults[88]. A study in mice showed that mice that were infected during the neonatal period were protected from gastritis and gastric cancer precursor lesions in spite of having increased bacterial loads while adult mice infected with *H. pylori* developed those lesions. Neonatally infected mice developed tolerance, were unable to induce T cell responses and were protected from T cell-mediated immunopathology[89]. In contrast to T_{reg} cells, Th17 cells play a crucial role in *H. pylori* clearance as suggested by vaccine studies[90,91]. However, *H. pylori* may utilize several mechanisms to induce T_{reg} responses while keeping a suboptimal level of Th17 cells in the host, which helps to establish a chronic infection. There is an increased recruitment of DCs in the gastric lamina propria of *H. pylori*-infected mice[92]. A study by Kao *et al*[93] showed that DCs stimulated with *H. pylori* inhibits the Th17 response and skew the response toward T_{reg} cells. This mechanism depends on development of T_{reg} cells with the required cytokines, TGF-β and IL-10, and this mechanism was independent of *H. pylori* virulence factors VacA and CagA. This study further showed that T_{reg} depletion enhanced the *H. pylori* specific Th17 response, and correlated with decreased bacterial colonization in mice[93]. In another mechanism of T cell suppression, *H. pylori* interfere with DC maturation process and convert immature DCs to tolerogenic DCs. Increased numbers of these semi-mature DCs were found in the chronically infected gastric mucosa of human *H. pylori* carriers. *H. pylori*-induced tolerogenic DCs were incapable of activating effector functions in naive T cells; however, these cells became very efficient in inducing T_{reg} and this process depended on DC derived IL-18 production[48].

Bone marrow-derived mesenchymal stem cells (BM-MSCs) also play an important role in the *H. pylori*-induced immunosuppressive response. Transplantation of BM-MSCs into the stomach of mice with *H. pylori* infection fostered significant stimulation of systemic and local IL-10-secreting T cells, which may inhibit other T cells. There was also an increased percentage of $CD4^+IL\text{-}10^+$ cells and $CD4^+CD25^+FoxP3^+$ cells in splenic mononuclear cells. BM-MSC-transplanted mice showed elevated T_{reg}/Th17 ratios[94]. These studies showed that *H. pylori* uses several mechanisms to skew the T cell response towards T_{reg} cells, which helps *H. pylori* to successfully establish a chronic infection.

EVASION OF HUMORAL RESPONSE

The majority of people infected with *H. pylori* develop a specific antibody response. This response is not normally enough to clear infection. Some studies suggest that infected children produce less antibodies, which may be concurrent with more T_{reg} cells and less activated $CD4^+$ cells to act as helper cells in the induction of B cell responses[95]. Although most or all infected individuals are thought to mount an antibody response to *H. pylori*, differences in this response have been noted between those who develop gastritis or duodenal ulcers compared to those who develop gastric cancer[96]. By examining patient serum antibody levels, infected individuals who developed gastritis or duodenal ulcers were shown to have a greater IgG response than those who developed gastric cancers. In turn, gastric cancer patients mounted a more vigorous IgA response than those with gastritis and duodenal ulcers. In another study of serum antibody responses to *H. pylori* in Japan, the authors suggested that a weak antibody response was linked to a high risk of developing gastric cancer by infected individuals[97]. Another study suggested that development of antibodies specific to virulence factors of *H. pylori* may be linked to gastric cancer[98]. In this study, gastric cancer patients were more likely to develop antibodies to CagA and heat shock protein B, while no significant differences were found in the levels of VacA specific antibodies between individuals with gastric cancer in comparison to other disease manifestations. These studies suggest that differences in humoral responses to infection may be linked to disease in infected individuals, but the mechanisms behind these differing responses remain elusive.

Although most people respond to *H. pylori* with a high serum antibody titer, this response is not efficient in reducing bacterial burden as evidenced by studies in mice that lack B cells and in various vaccine studies. In a study of mice lacking B cells, mice were protected against *H. pylori* challenge suggesting that the humoral response is dispensable in protection against *H. pylori*. To further support this study, another B cell knockout study showed that with an *H. pylori* urease vaccine, mice deficient in B cells had equal protection as wild type mice and stomach $CD4^+$ T cells were equal in both mouse strains[99]. This study further indicated a correlation between the amount of T cells in the gastric mucosa and the level of protection, again suggesting that the humoral response is less crucial in protection against *H. pylori*. In addition to the viewpoint that protection against *H. pylori* challenge is independent of the B cell response, there is also compelling evidence that antibodies elicited against *H. pylori* may be harmful to the host. One group has shown in mice that specific antibody responses to *H. pylori* may actually aid in bacterial colonization and impair other immune responses against *H. pylori*[100]. This study showed that T cells, not B cells, were responsible for gastritis induced by infection and suggested the possible role for antibodies in inhibiting host resistance to infection in showing improved elimination of bacteria in the absence of antibodies in B cell deficient mice. B cell deficient mice were able to clear bacteria at 12-16 wk post infection, whereas wild type mice still had a robust infection coupled with gastritis at this time point. Another compelling study showed that *H. pylori* evade antibody mediated recogni-

tion because of a lack of surface binding of host elicited antibodies[101]. This study consisted of incubating bacteria with sera from patients who had detectable antibody responses to *H. pylori*. There was very little binding of antibodies to the surface of the bacteria, thus indicating another way the host immune response may be evaded.

Another intriguing aspect of the humoral response to *H. pylori* are reports of autoantibodies that are induced during infection. These antibodies were against self-epitopes and potentially caused damage in the host. For instance, one group showed that *H. pylori* induced antibodies against parietal cells in the stomach, which persisted after bacterial eradication and were linked to intestinal metaplasia[102]. In support of these results, another study examined autoantibodies in infected patient sera, revealing a prevalence of autoantibodies during gastritis associated with gland destruction and stomach atrophy[103]. There has also been indication of disease-specific autoantibodies induced by *H. pylori* infection. A study in duodenal ulcers showed that autoantibodies impair gastric secretory functions[104]. Decreased acid secretion, but increased gastrin were seen along with increased gastritis. This was shown in 20% of duodenal ulcer patients coupled with a more severe disease manifestation. Likewise, detrimental effects of autoantibodies have been seen in gastric cancer as well. In a small panel of gastric cancer patients, spleen cells were isolated, immortalized with human hybridoma technologies, which allowed for characterization of 11 *H. pylori* induced autoantibodies that reacted with gastric cancer cell specific proteins[105]. Several of these antibodies stimulated gastric cancer cells to proliferate, interestingly enough, in contrast to normal epithelial cells. These studies represent an intriguing aspect to *H. pylori* immune evasion in humans that may still require further investigation to clarify the mechanisms involved.

GENOMIC DIVERSITY IN IMMUNE EVASION

H. pylori is one of the most genetically diverse bacterial species. Initial insights into this diversity were apparent when the first strains of *H. pylori* were first sequenced. When 26695 and J99 *H. pylori* strains were compared at the genome level, it was observed that 6% of the genome represented strain specific genes, which are mostly located in a region now referred to as the plasticity zone[106]. Since then, multiple other strains have supported the observation that such diversity occurs at the size of the genome, gene arrangement and alleles. The extensive genetic diversity of *H. pylori* is the result of high mutation rates and high recombination frequency[107,108]. An important virulence factor of *H. pylori* is encoded in a 37-kB segment of DNA referred to as the *cag* PAI. Since it was discovered, *cag* PAI is perhaps the most studied region of the *H. pylori* genome. An array of *H. pylori* isolates have been noted to differ in the rate with which they have the *cag* PAI in their genome[109], which was recently supported by a study that included 877 isolated from diverse populations and which highlighted the variability in the carriage of *cag* PAI by *H. pylori* strains. This *cag* PAI mostly encode an array of structural constituents of a bacterial T4SS in addition to a 128 kDa effector protein, CagA. When *H. pylori* adheres to GECs, CagA is translocated *via* the T4SS into the host cell cytoplasm where it becomes phosphorylated by host cell kinases and interacts with various signaling proteins[110,111]. As a result of the multiple interactions of CagA with host cell signaling proteins, multiple processes are affected leading to cell transformation. This effector protein also has a significant level of diversity, particularly in the C-terminal EPIYA repeat motifs where CagA is phosphorylated once it is inside the host cell. These EPIYA motifs differ between Asian and Western isolates. An interesting study of *H. pylori* isolates from experimentally infected mice and non-human primates showed that they have rearrangements in CagY of the T4SS[112], which in turn result in gain or loss of function in the *H. pylori* T4SS. These observations may be reflective of the overall variability in *H. pylori* strains, which in turn contribute to immune escape and the establishment of chronic infection.

IMMUNE SYSTEM BASED THERAPY

To get an effective immune response against *H. pylori*, T cells must be activated into an effector state. Co-stimulatory and inhibitory molecules regulates T-cell activation, and works as "immune checkpoints". *H. pylori* have been shown to upregulate B7-H1 expression and downregulate B7-H2 expression on GEC and, thus, not only decrease the effector T cell response but also alter T cell sub-population balances by increasing T_{reg} and decreasing Th17 cell numbers[63-65]. This novel information may permit control *H. pylori* infection by targeting the inhibitory receptor/ligand axis. The anti-PD-1 monoclonal antibody nivolumab, (also known as MDX-1106 or BMS-936558) and lambrolizumab have already been used in a phase I trial and have shown promising results in patients with melanoma and other cancers[113-115], and conceivably could have an effect in the outcome of *H. pylori* infection and/or immunization. Since we have shown previously that *H. pylori* uses mTOR/p70 S6 kinase pathway to downregulate B7-H2 expression[65], another approach to control *H. pylori* could involve the use of rapamycin, which inhibits this pathway. Analogues of this drug have been used already and shown promising results in renal cell carcinoma and breast cancer treatments[116]. The immune modulatory properties of this bacterium could be exploited therapeutically to control other diseases. For example, recombinant HP-NAP has been shown to be beneficial in the treatment of allergic diseases and immunotherapy of cancer due to its ability to induce Th1 responses. It was shown to inhibit the growth of bladder cancer[117]. HP-NAP has also been used as an immune modulating agent to suppress Th2 responses in allergic asthma and *Trichi-*

nella spiralis infection[118,119].

CONCLUSION

H. pylori has been co-existing with human host for at least 30000 years[120]. During this long time of co-existence the bacteria has undergone evolutionary adaptation and established a comfortable niche in the human host. Unlike most other pathogenic bacteria which are cleared by the host adaptive immune response, *H. pylori* successfully establishes a persistent infection in its host in spite of the presence of vigorous innate and adaptive immune response. *H. pylori* evolved an array of mechanisms to evade both innate and adaptive immune responses. Host mediated immune response not only fails to clear the bacteria but also helps the bacteria for colonization by proving increased availability of adhesion places such as MHC Ⅱ and CD74, both of these components are induced by IFN-γ and IL-8 during *H. pylori* infection[121,122]. *H. pylori* virulence factors VacA, HP-NAP, Cag T4SS have been shown to cause damage in the gastric epithelium which results in peptic ulcer or even gastric cancer, if left untreated. Bacterial virulence factors together with host factors determine the severity of disease. Though multiple studies have examined how the bacteria interact with its host there is still a lack of clear knowledge about how it avoids host mediated immune responses. Furthermore little is currently known about the role of T cell subsets in controlling *H. pylori* infection and associated immunopathogenesis, particularly in humans. A better understanding of the mechanisms it uses to evade or subvert host immune response is crucial to design a therapeutic or a successful vaccine to eliminate this highly prevalent and deadly pathogen.

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