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Inflammation, Immunology and Vaccines for *Helicobacter pylori* Infection

Alojz Ihan[†], **Irina V. Pinchuk**[+], and **Ellen J. Beswick**[‡]

[†]Institute of Microbiology and Immunology, Faculty of Medicine, University of Ljubljana, Zaloška 4, 1000 Ljubljana, Slovenia

[+]Department of Internal Medicine, Division of Gastroenterology and Hepatology, University of Texas Medical Branch, Galveston, Texas 77555

[‡]Department of Molecular Genetics and Microbiology, University of New Mexico, Albuquerque, NM 87131

Abstract

The immune response to *H. pylori* is a multifaceted group of mechanisms involving responses that are both protective and damaging to the host. The innate and the adaptive immune responses lead to damaging inflammatory responses, but these responses are also kept in check, allowing for persistence of many infections. Thus, developing new therapeutics and effective vaccines against *H. pylori* has proven to be arduous. In this manuscript, we will examine the advances in knowledge made in the past year in understanding the host immune response to *H. pylori* and progress towards developing a vaccine.

The Innate Response to *H. pylori*

The host innate immune system plays a key role in the initiation and the subsequent progression of the *H. pylori* associated pathogenesis. Gastric epithelial cells (GECs) are primary target for *H. pylori* infection, and actively contribute to the innate immune responses via signaling through pattern recognition receptors, such as Toll-like receptors (TLRs). GECs are the first point of contact for *H. pylori* and express TLRs that may activate an innate immune response. Although LPS is the classical bacterial ligand for TLR4, *H. pylori*-derived LPS reported to signal through TLR-2 and have low binding affinity for the TLR4. To further examine this, one study showed that *H. pylori* enzymes, LpxE and LpxF, desphosphorylate the lipid A of its' LPS, leading to a decrease in recognition by TLR-4 (1). In another suggested mechanism of immune evasion, *H. pylori* was shown to inhibit macrophage release of nitric oxide in response to *H. pylori* LPS in a mouse model of infection (2). *H. pylori* LPS was also shown to suppress TLR-4 signaling, but enhance IL-12 and IL-18 production (3), which was suggested to be linked to the chronic inflammation commonly seen during infection. In further support for the role of *H. pylori* LPS signaling through TLR-2 instead of TLR-4, one group demonstrated that upon TLR-2 activation by LPS derived from *H. pylori* inhibited the TRIB3 protein, which controls TLR-2-mediated NF-κB signaling, thus leading to increased NF-κB signaling (4). A further role TLR-2 was shown in addition to TLR-5 expression by *H. pylori* on THP-1 monocytic leukemia cells resulted in a shift from cagPAI-dependent to cagPAI- independent signalling leading to the secretion of IL-8 and TNF-α (5). In NK cells, TLR-2 was shown to be activated by *H. pylori* lipoprotein HpaA, leading to IFN-γ production in an IL-12 dependent manner (3, 6). In

Correspondence: Dr. Ellen J. Beswick, MSC08 4660, 1 University of New Mexico, Albuquerque, NM 87131-0001, ebeswick@salud.unm.edu, ph 505-272-3383, fax 505-272-9675.

further analysis of TLR-2 activation by *H. pylori*, urease was shown to activate TLR-2 on B cells, inducing autoantibodies and suggesting a link to autoimmune disorders (7). Also of relevance clinically, a recent epidemiologic study demonstrated that genetic polymorphisms in TLR-5 may contribute to the *H. pylori*-associated gastric cancer in Chinese population (8).

Inflammation is a crucial player in the *H. pylori* immune response. During inflammation resulting from infection, bone marrow derived mesenchymal stem cells are recruited to the gastric mucosa. These cells are thought to be underlying promoters of gastric cancer. A recent study shows that *H. pylori* infection of gastric epithelial cells induces migration of mesenchymal stem cells, which was dependent upon NF-κB activation and TNF-α production in an *in vitro* model (9). These findings were further substantiated in a mouse model of infection where accumulation of bone marrow derived stem cells were found in the gastric mucosa following *H. pylori* infection and 25% of dysplastic lesions included bone marrow derived stem cells in the mouse model (10).

The Adaptive Response to *H. pylori*

H. pylori employ a variety of mechanisms to inhibit the T cells response and persist in the gastric mucosa. Treg are induced during infection, which express the FoxP3 transcription factor and inhibit other T cell responses by producing IL-10 and TGF-β. Tregs are induced when TGF-β is present, along with PDL-1 expression on antigen presenting cells (11, 12). A unique feature of the gastric epithelium is the ability to act antigen presenting cells in expressing class II MHC and co-stimulatory and co-inhibitory molecules. Gastric epithelial cells were shown to produce TGF-β after exposure to *H. pylori* (12). *H. pylori*-induced TGF-β was shown to inhibit $CD4^+$ T cell proliferation and lead to Treg development, suggesting a mechanism that it uses to subvert the host response and persist in the gastric mucosa. Another novel mechanism of Treg development during *H. pylori* infection was established in the mouse model where IL-18 was shown to be required for Treg development and was produced by dendritic cells during infection (13). *H. pylori*-induced Tregs were also shown to provide protection from airway inflammation in an asthma model (14).

In continued analysis of the T cell response during infection, a closer look at the Th1 response during infection was examined. Tbet expressing $CD4^+$ T cells that produce IFN-γ have long been described during *H. pylori* infection, and are suggested to be responsible for some host damage seen during infection. However, Th1 cells may be inhibited to allow for persistence of infection (12, 15). One group demonstrated that the stromal extracellular matrix inhibited dendritic cell responses, and in turn damped the Th1 response to infection (15). Although *H. pylori*-infected macrophages were shown to induce Th1 cells in co-culture assays (16), if these cells are inhibited in the stroma, this may be another means of *H. pylori* persistence in the gastric mucosa.

More recently, RORγ, IL-17 expressing Th17 cells have emreged as an important participant in the pro-inflammatory immune response to *H. pylori* infection. *H. pylori*-infected macrophages were found to produce IL-6, TGF-β, and IL-23 (16), which are required for Th17 phenotype development and maintenance. In a *H. felis* model, myeloid differentiation primary response gene 88 (MyD88) was required for Th17 development (17). MyD88 is a universal adapter protein used by TLRs to activate NF-κB signaling, suggesting a role for TLR activation in Th17 development. In further progress toward understanding the Th17 response, bacterial motility was linked to the Th17 response (18). *H. pylori* that were deficient in motility, but could still colonize, show decreased ability to recruit $CD4^+$ T cell and lacked a Th17 response in the mouse model of infection.

In the clinical setting, Tregs were shown to be increased in a cohort of *H. pylori*-infected children, where the number of FoxP3 expressing cells and the level of TGF-β present in the gastric mucosa was positively correlated with the density of *H. pylori* (19). Another study further confirmed a predominate Treg response in children, and further showed that infection in children induces less Th17 than in adults (20). However, the Treg response in adults should not be overlooked, as a recent study also shows Tregs infiltrating the infected gastric mucosa with concurrent expression of the inhibitory receptor, PD-1 (21).

The B cell response to *H. pylori* may sometimes be overlooked. However, one group showed that *H. pylori* enhanced expression of CXCL13 in the gastric mucosa (22). CXCL13 is known to regulate B cell homing and in this study *H. pylori*-infected patients had significantly more CXCR13 expression in the gastric antrum than uninfected patients. This study also correlated with the expression of the receptor for CXCL13, CXCR5. CXCR5 was also found in conjunction with CD20 positive lymphocyte aggregates, suggesting a role for B cells in the host response to *H. pylori* infection. Another recent study examined murine B cells in response to *H. pylori* urease (7). $CD5^+$ B1-a cells were found to produce autoantibodies when exposed to *H. pylori* urease, which was dependent on TLR2, suggesting that *H. pylori* urease may activate TLR2 signaling on B cells.

H. pylori virulence factors induction of immune responses

The cytotoxin associated pathogenicity island (cagPAI) virulence factor has been intensely studied in the past decade due to the immune responses it invokes and its link to carcinogenesis. Recently, CagA has been termed a oncoprotein due to its' intracellular activities that lead to dysregulation of cell division (23). Once inside cells, CagA is phosphorylated by src tyrosine kinases. CagA proteins from different strains have different amounts of EPIYA motifs, which allow for different levels of phosphorylation. The number of EPIYA motifs has been suggested to be directly linked to the risk of carcinogenesis (24). CagA was shown to increase motility of gastric epithelial cells (25), suggesting the potential for a metastatic role. CagA was also shown to induce overexpression of microRNAs, leading to increased NF-κB and Erk1/2 signaling, targeting, and inducing epithelial-mesenchymal transition and intestinal metaplasia of gastric epithelial cells (26). In yet another new finding, CagA was shown to induce spermine oxidase in gastric epithelial cells, which when metabolized leads to H_2O_2, apoptosis, and DNA damage (27). A subpopulation of the gastric epithelial cells in this study was found to be resistant to apoptosis so the enhanced DNA damage may increase the likelihood of carcinogenesis. Another study demonstrated the importance of CagA in gastric neoplasia by showing that CagA specific T cells from mice vaccinated with CagA injected into T cell deficient mice infected with *H. pylori* induced pre-neoplastic immunopathology.(28). Another approach to CagA vaccination in this study also let to sensitization to *H. pylori* rather than protection, but a tolerization by injecting *H. pylori* sonicates in conjunction with CD40L antibodies in neonates led to protection against gastric pathologies.

The vacuolating cytotoxin A (VacA) virulence factor has long been associated with host damage by forming pores in host cell membranes, disrupting membrane trafficking and inducing apoptosis. One study described the mechanisms associated with apoptosis to include VacA-induced decreases in known cellular survival proteins, Stat3 and Bcl-2 family proteins (29). Similarly, another group showed that the pro-apoptotic member of the Bcl-2 family, Bax, was induced through VacA activation of mitochondrial fission machinery within the cell (30). A recent study further expanded the knowledge of the role of VacA host cell damage by a detailed examination of the death mechanisms, showing a caspase independent process that included the histone-binding protein high mobility group box 1, which is consistent with known necrosis pathways (31). This study further suggested that the

end result of epithelial cell necrosis is release of inflammatory proteins that contribute to pathogenesis.

H. pylori cell division-related gene A (cdrA) was shown to induce NF-κB activation and IL-8 production by AGS cells (32). This finding was correlated to strains in human samples where expression of cdrA was found in 90% of Japanese isolates, but only 17% of American isolates, which was accompanied by higher levels of mucosal IL-8 in the cdrA positive samples compared to the cdrA negative samples.

Urease plays an important role in *H. pylori* colonization and survival in the acidic environment of the stomach. In one protective mechanism of the host, CD46, C3b/C4b binding compliment regulator, was shown to bind to *H. pylori*, inhibit urease activity, and thus, the ability of the bacteria to survive in an acidic environment (33). The urease B subunit was recently shown to lead to Th17 responses in the mouse model of *H. pylori* infection (34). When recombinant urease B was incubated directly with mouse splenic lymphocytes, IL-17 producing cells were increased and when macrophages were incubated with recombinant urease B, IL-6 and IL-23 were produced to support Th17 development.

H. pylori lipopolysaccharide (LPS) has been shown to induce weaker immune responses than LPS from other bacteria. Particularly, LPS from *H. pylori* did not induce strong IL-1β, IL-6, or IL-8 responses (35) as other bacterial LPS does. *H. pylori* LPS was also shown to induce little NF-κB activation through TLR4, but was shown in this study to induce IL-12 and IL-18 responses, which are thought to be pro-inflammatory. This is in contrast to another study that showed a lack of IL-12 and IL-2 induction by lymphocytes incubated with *H. pylori* LPS, which was accompanied by decreased cytotoxic activity by lymphocytes incubated with *H. pylori* LPS compared to that of *E. coli* (36).

Progress in Vaccine Development to *H. pylori*

The beginning of 2011 was marked by a promising publication in the field of *H. pylori* vaccine developement made by Moss et al (37). They used a computational method to predict novel T-cell epitopes. The multi-epitope vaccine was administered intranasally or intramuscularly to *H. pylori*-infected mice, followed by a boost with the peptides themselves formulated in liposomes with CpG oligonucleotides and heat labile enterotoxin. The vaccine induced a broad immune response, as determined by IFN-γ production, and led to a sterilizing immunity 32 weeks after challenge in 5 of 19 mice.

Another promissing vector platform for expression of *H. pylori* antigens was published in the beginning of 2011 by Iankov, *et al.* (38). They produced a measles virus (MV) vaccine strain encoding the *H. pylori* neutrophil-activating protein (NAP). Nine months post vaccination all animals immunized with MV strains expressing the secretory NAP antigen developed a strong humoral immunity against NAP within 2–4 weeks. By using IFN-γ ELISpot assay, they also confirmed affective NAP-specific cell-mediated immunity. Their experiments importantly demonstrated that immunization with a live replication competent vaccine expressing *H. pylori* molecules (NAP or potentially CagA, VacA etc) induced not only robust antibody production but also distinctive cell-mediated response against H. pylori antigens.

Improved efficacy of vaccines may be achieved in new trials of vaccine formulations that include multiple antigens and use methods to optimize cellular immunity. An approach made by Chen J et al (39) used a *H pylori* oipA gene encoded construct co-delivered by IL-2 gene encoded construct and B subunit heat-labile toxin of Escherichia coli gene encoded construct. With intradermal co-delivery of adjuvant(s), they were able to shift the immune response from being Th2 to being Th1-biased, which resulted in a greater reduction in

bacterial load after *H. pylori* challenge. A similar approach used Salmonella vector construct that expressed fusion proteins complexed with *H. pylori* CagA, VacA and UreB in different arrangements (40). Oral therapeutic immunization significantly decreased *H. pylori* colonization in the stomach; protection was related to combination Th1, serum IgG and mucosal IgA responses.

Guo L et al (41) used an Escherichia coli expressed fusion protein construct of cholera toxin B subunit and an UreA epitope of *H. pylori* urease A vaccine had good immunogenicity and immunoreactivity and could induce specific neutralizing antibodies, however the efficieny of the vaccine should be confirmed by a sterilizing immunity trial since urease vaccine targets had a long history of rather disappointing results. Neverthless, it is worth it to mention an epitope urease vaccine developed by Chen S et al (42). The UreB was effectively expressed as food-grade antigen in Lactococcus lactis where the achieved percentage of recombinant antigen was estimated to be 7% of total soluble cellular proteins. Simmilar UreB gene expression, but in peanut, was achieved by Yang CY et all (43) where UreB gene was transformed into peanut embryo leaflets by Agrobacter-mediated method. Both approaches could serve as alternative vaccine strategies for preventing *H. pylori* infection.

It is also worth mentioning some vaccination experiments not directed towards novel approaches in vaccine production, but being important to further elucidate vaccination response against *H pylori*. In a fascinating work DeLyria, et al (44), IL-17A and IL-17A receptor knockout (KO) mice were immunized with *H. pylori* sonicate and with cholera toxin as adjuvant. Surprisingly, despite the previous demonstration that IL-17 antibody-mediated neutralization during challenge of mice compromises the protective immune response (45), the complete absence of IL-17A or its receptor did not significantly impact the ability of the murine host to develop vaccine-induced protective immunity against *H. pylori* or *H. felis*. Although the IL-17 response may be important for the eradication of the bacteria, as previously observed, there are multiple mechanisms for activating vaccine-based protective inflammatory responses against *H. pylori* and employ compensatory mechanismsof immunity.

In conclusion, progress in vaccine deveopment has been made in the past year. Several new approachs were taken, including novel T cell epitopes and virulence factors delivered with an IL-2 gene encoded construct. *H. pylori* virulence factor vaccines continue to be effective in mouse models, including urease, NAP, and OipA. Surprisingly, IL-17 was not shown to play an important role in protective immunity against *H. pylori*.

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