

Relation *Helicobacter pylori* with Pathogenesis of Stomach and Immune Responses

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ABSTRACT

Background: *Helicobacter pylori*, a member of *Epsilonproteobacteria*, is a Gram-negative microaerophilic bacterium that colonizes gastric mucosa of about 50% of the human population. Although most infections caused by *H. pylori* are asymptomatic, the microorganism is strongly associated with serious diseases of the upper gastrointestinal tract such as chronic gastritis, peptic ulcer, duodenal ulcer, and gastric cancer, and it is classified as a group I carcinogen. The prevalence of *H. pylori* infections varies worldwide. prevalence among middle-aged adults is over 80 percent in many developing countries, as compared with 20 to 50 percent in industrialized countries. The infection is acquired by oral ingestion of the bacterium and is mainly transmitted within families in early childhood, Humans can also become infected with *Helicobacter heilmannii*, a spiral bacterium found in dogs, cats, pigs, and nonhuman primates.

Conclusion: *H. pylori* infection stimulates the reaction of autoantibodies with gastric epithelial cells, and this leads to gastritis. These autoantibodies can be directly induced to epithelial cells by activating complement, inducing apoptosis or provoking an antibody-dependent cytotoxic reaction resulting in subsequent tissue destruction.

Keywords: *Helicobacter pylori*, IgG & IgA & CD4+ T Cell Responses.

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INTRODUCTION

Helicobacter pylori, a member of *Epsilonproteobacteria*, is a Gram-negative microaerophilic bacterium that colonizes gastric mucosa of about 50% of the human population. Although most infections caused by *H. pylori* are asymptomatic, the microorganism is strongly associated with serious diseases of the upper gastrointestinal tract such as chronic gastritis, peptic ulcer, duodenal ulcer, and gastric cancer, and it is classified as a group I carcinogen. The prevalence of *H. pylori* infections varies worldwide (1). *Helicobacter pylori* is a spiral-shaped Gram-negative bacterium that colonizes the human stomach and can establish a long-term infection of the gastric mucosa, a condition that affects the relative risk of developing various clinical disorders of the upper gastrointestinal tract, such as chronic gastritis, peptic ulcer disease, mucosa-associated lymphoid tissue (MALT) lymphoma, and gastric adenocarcinoma.

H. pylori presents a high-level of genetic diversity, which can be an important factor in its adaptation to the host stomach and also for the clinical outcome of infection. There are

important *H. pylori* virulence factors that, along with host characteristics and the external environment, have been associated with the different occurrences of diseases (2). The

prevalence among middle-aged adults is over 80 percent in many developing countries, as compared with 20 to 50 percent in industrialized countries. The infection is acquired by oral ingestion of the bacterium and is mainly transmitted within families in early childhood (3), (4). Humans can also become infected with *Helicobacter heilmannii*, a spiral bacterium found in dogs, cats, pigs, and nonhuman primates (5).

Pathogenesis

The gastric mucosa is well protected against bacterial infections. *H. pylori* is highly adapted to this ecologic niche, with a unique array of features that permit entry into the mucus, swimming and spatial orientation in the mucus, attachment to epithelial cells, evasion of the immune response, and, as a result, persistent colonization and transmission. The *H. pylori* genome (1.65 million bp) codes for about 1500 proteins (6), (7)

Among the most remarkable findings of two *H. pylori* genome-sequencing projects were the discovery of a large family of 32 related outer-membrane proteins (Hop proteins) that includes most known *H. pylori* adhesins and the discovery of many genes that can be switched on and off by slipped strand mispairing mediated mutagenesis. Proteins encoded by such phase-variable genes include enzymes that modify the antigenic structure of surface molecules, control the entry of foreign DNA into the bacteria, and influence bacterial motility. The genome of *H. pylori* changes continuously during chronic colonization of an individual host by importing small pieces of foreign DNA from other *H. pylori* strains during persistent or transient mixed infections (8),(9).

Considerable experimental evidence indicates that the *H. pylori* genotype is a substantial factor determining the type of induced disease (10). However, there are also some host factors, such as polymorphism of the IL-1 β , which influences gastric acid secretion, or polymorphism of the CYP2C19, which is the main enzyme metabolizing PPI (proton pump inhibitor), that are associated with the risk of gastric cancer development (11). Some

studies indicate that environmental factors, such as nutrition, should additionally be taken into account (12), (13).

Antibiotic resistance of *H. pylori* has reached alarming levels worldwide, prompting an urgent search for more efficient treatments. A recent systematic review and meta-analysis of 178 studies demonstrated an increased rate of primary and secondary *H. pylori* resistance in six World Health Organization Regions (14), (15). Probiotics are defined as “live microorganisms that, when administered in adequate amounts, confer a health benefit on the host” (16). They have been used in the prevention and treatment of some gastrointestinal disorders, such as diarrhea, irritable bowel syndrome, and inflammatory bowel disease. Administration of probiotics brings beneficial effects to host microbiota, enhances the immune system, and shows inhibitory effects on pathogens (17).

Immune Responses to *Helicobacter pylori* Infection

Helicobacter pylori (*H. pylori*) infection is one of the most common infections among individuals worldwide (18). After entering the stomach, these aerobic spirochetes penetrate the gastric mucosal layer but do not cross the epithelial barrier of the stomach (19) they are considered a non-invasive species. Most *H. pylori* organisms live freely in the mucosal layer, but some organisms adhere to the apical surface of gastric epithelial cells, and very few have been shown to invade epithelial cells (20).

Upon infection, *H. pylori* uses urease and α -carbonic anhydrase to generate ammonia and HCO₃²⁻ as this mitigates the effects of low pH (21), (22). Thanks to its flagella and distinctive shape, it has the ability to penetrate the mucus layer. *H. pylori* null mutant, but the defect in the production of flagella is that it is unable to colonize gnotobiotic piglets (23). Once established in the inner mucus layer, several outer membrane proteins, including BabA, Saba, AlpA, AlpB and HopZ, can mediate bacterial adhesion to gastric epithelial cells. It modulates gastric epithelial cell behavior resulting in cell polarity loss, release of nutrients and chemokines (eg interleukin (IL)-

8), and regulation of acid secretion by controlling gastrin and H⁺/K⁺ ATPase (24), (25).

Cellular responses are related to the humoral immune response in humans infected with *H. pylori*. Patients' IgA and IgG antibodies are chronically directed towards many different *H. pylori* antigens (26). The local antibody response directed to *H. pylori* antigens can also be detected with chronic *H. pylori* infection. These subjects had higher frequencies of total IgA and IgM-secreting cells compared with the uninfected, while the frequencies of IgG-secreting cells were almost the same in the different groups (27). It is noteworthy that *H. pylori* infection stimulates the reaction of autoantibodies with gastric epithelial cells, and this leads to gastritis. These autoantibodies can be directly induced to epithelial cells by activating complement, inducing apoptosis or provoking an antibody-dependent cytotoxic reaction resulting in subsequent tissue destruction (28).

IgA Response

IgA is a major defense mechanism that excludes symbionts and pathogens from the mucosal surface (29). Mucosal IgA includes antibodies that recognize antigens with high and low affinity binding patterns. In general, high-affinity IgA neutralizes invading pathogens and microbial toxins, high-affinity IgA is believed to appear in Peyer's patches (PPs) and mesenteric lymph nodes (MLNs) of mesenteric B cells that are stimulated through T-cell-dependent pathways, while from the likely appearance of low-affinity IgA in PPs, MLNs, and lamina propria from B cells is stimulated via T-cell-independent pathways (29).

The IgA response is strongly induced by the presence of commensal microbes in the gut (30), (31) and has been shown to enhance the maintenance of appropriate bacterial communities in certain parts of the intestine, unlike in the lungs, vagina and most of the gastrointestinal tract, healthy mammalian stomachs produce a very low proportion of globulin receptors. Polymeric immunoglobulin (pIgR) (32), (33) this is the receptor that

mediates the transport of immunoglobulin A into the lumen of the gastrointestinal tract. Several studies in humans with *H. pylori* have shown that core pIgR expression by the gastric epithelium can be upregulated in response to gastritis due to increased local IFN- γ production (34).

However, although pIgR expression was significantly increased and plasma cell IgA infiltrated in response to *H. pylori* infection, there was no concomitant increase in gastric IgA secretion, a mono-non-secretory IgA that predominates in the stomachs of *H. pylori* infected individuals (35). Thus, the IgA present in the gastric lumen will be unstable and prone to degradation by proteases (36).

IgG Response

Some degree of systemic exposure to enteric commensal bacteria and an associated systemic immune response appears to be well tolerated and harmless and common in healthy humans where antibody responses can be detected against bacteria and commensal fungi in the gut, most *H. pylori* infection develop a systemic anti-*H. pylori* IgG response (37). Recently the expression of neonatal Fc receptors in gastric epithelial cells has been explored, and this receptor has been shown to transport IgG to gastric secretion. These results indicate that *H. pylori* IgG antagonists can reach the gastric mucosa as well as exert some antibacterial and/or pro-inflammatory activities (36).

CD4+ T Cell Responses

As *H. pylori* is an extracellular bacterium, it is anti-*H. pylori*-specific CD8⁺ T-cell responses are insufficient to protect the host from this pathogen. CD4⁺ T-cell responses within PPs and MLNs are initiated by DC capture, processing and antigen presentation to naive T cells in PPs and MLNs in the stomach. Steady-state, mucosal CD4⁺ T cells are tolerant to bacteria-derived antigens (38). Remarkably, systemic CD4⁺ T cells are not tolerant to germ-derived antigens and maintain a naive state for these antigens (39).

It has recently been suggested that antigen-specific intestinal IgA plays an important role in inhibiting systemic CD4+ T-cell responses

to commensal antigens by providing immune exclusion (38).

CONCLUSION

H. pylori infection stimulates the reaction of autoantibodies with gastric epithelial cells, and this leads to gastritis, these autoantibodies can be directly induced to epithelial cells by activating complement, inducing apoptosis or provoking an antibody-dependent cytotoxic reaction resulting in subsequent tissue destruction. Cellular responses are related to the humoral immune response in humans infected with *H. pylori*, Patients' IgA and IgG

antibodies are chronically directed towards many different *H. pylori* antigens. systemic CD4+ T cells are not tolerant to germ-derived antigens and maintain a naive state for these antigens. It has recently been suggested that antigen-specific intestinal IgA plays an important role in inhibiting systemic CD4+ T-cell responses to commensal antigens by providing immune.

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