EDITORIAL

Helicobacter pylori and its Interaction with Gastric Microbiota and Host Genetics in Gastric Cancer

Kashi N Prasad

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Introduction

Approximately 20–25% of all cancers are linked to infectious agents like viruses, bacteria, and parasites. *Helicobacter pylori* has been strongly linked to gastric cancer. So far, gastric cancer is identified as the fifth most common cancer and the third most common cause of cancer-related death in humans. The World Health Organization declared *H. pylori* as a class I gastric carcinogen in 1994. However, it is estimated that only 1–2% of *H. pylori*-infected populations develop gastric cancer, thus raising the question about bacterial strain specificity, i.e., all *H. pylori* strains may not have carcinogenic potential. Host genetic variability, *H. pylori*-induced altered gastric microbiota, and environmental factors play the important role in the development of gastric cancer.

H. pylori could persist for decades in the harsh stomach environment, where it damages the gastric mucosa by inducing inflammation. Earlier studies from the West implicated cytotoxin-associated gene (cagA)-positive *H. pylori* strains with peptic ulcer disease (PUD) and gastric cancer.[1] However, studies from India and other developing countries showed that cagA-positive *H. pylori* strains were detected in almost equal proportions in patients with gastric cancer, PUD, and functional dyspepsia, thus contradicting the Western literature. Scientists started looking for other virulence markers. A well-known virulent marker of *H. pylori* is cag pathogenicity island (cagPAI), which encodes a type-IV secretory system (T4SS) forming a syringe-like structure to translocate its cagA protein as well as peptidoglycan directly into host gastric epithelial cells. The cagPAI is a 40-kb genomic fragment consisting of 32 genes and the island is not a conserved entity. It is susceptible to various genetic rearrangements occurring within and outside the island. An intact cagPAI has therefore been thought to contribute toward the full inflammatory power of *H. pylori*. Certain genes of cagPAI such as *cagA*, *cagE*, *cagT*, *cagM*, and *cagL* have extensively been studied and their role in gastric carcinogenesis has been postulated. *cagE, cagT*, and *cagM* participate in T4SS for translocation of CagA and peptidoglycan into the gastric epithelial cells. CagA is considered an oncoprotein, and its translocation inside gastric epithelium is thought to be an important step in gastric carcinogenesis. CagA induces the production of pro-inflammatory cytokine IL-8 by gastric epithelial cell that leads to the development of gastritis. It also enhances cell proliferation and cell motility through signal transduction after its internalization into the cells. CagL is a pilus protein of *H. pylori* that interacts with host cellular α5β1 integrins through its arginine-glycine-aspartate motif, guiding proper positioning of the T4SS and translocation of CagA. Deletion or sequence variations of *cagL* significantly diminish the ability of *H. pylori* to internalize the CagA oncoprotein, thus reducing the secretion of IL-8 by the host cell.

Department of Microbiology, Apollomedics Super Speciality Hospital, Lucknow, Uttar Pradesh, India

Corresponding Author: Kashi N Prasad, Department of Microbiology, Apollomedics Super Speciality Hospital, Lucknow, Uttar Pradesh, India, e-mail: kashinprasad@gmail.com; drkashinath_p@apollohospitals.com

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CagA-dependent signaling leads to cell proliferation; hence, the virulence of *H. pylori* strain depends on how efficiently it is capable of translocating its CagA oncoprotein into the gastric epithelium. We observed that CagL with D58K59 amino acid polymorphisms had 3.8-fold increased risk for the development of gastric cancer.[2] We investigated the presence of *cagE*, *cagT*, *cagM*, and *cagL* genes in cagA-positive *H. pylori* isolates. Strains that harbored all these genes were defined as having fully functional cagPAI. Strains lacking any of these genes and all of these genes were defined as partially functional and completely dysfunctional, respectively. Interestingly, we observed that patients infected with *H. pylori* strains having fully functional cagPAI had 10-fold increased risks for the development of intestinal-type gastric cancer.[3] Further, we observed that *H. pylori* having fully functional cagPAI-induced over expressions of ADAM-10 (a disintegrin and metalloprotease), ADAM-17, and inflammatory cytokines IL17A and IL23. ADAMs are multifunctional proteins involved in various biological events, such as cell adhesion, cell fusion, cell migration, membrane protein shedding, extracellular matrix degradation, and proteolysis. Thus, overexpressions of ADAMs modulate tissue microenvironment and facilitate cell proliferation and progression to gastric cancer both in autocrine and paracrine manners. Overexpressions of ADAMs and cytokines IL17A and IL23 strongly correlated with intestinal-type gastric cancer in the presence of *H. pylori* infection.[4]

Another microbe that harbors the stomach is Epstein-Barr virus (EBV). It is a ubiquitous herpes virus that has emerged as an agent of gastric cancer. Both *H. pylori* and EBV infect human stomach, but it remains unclear whether both the pathogens compete or complement each other in the stomach. *H. pylori* and EBV coinfection was almost 40% in our gastric cancer patients.[5] Most of the *H. pylori*-positive patients harbored latent EBV infection. Expression of transforming growth factor-beta 1 (TGF-β1), a trigger for lytic EBV infection, was lower in *H. pylori*-infected than *H. pylori* non-infected patients. This unique observation suggests that *H. pylori* suppresses the expression of TGF-β1, thus preventing lytic

EBV infection and maintaining the latency of EBV.[6] Whether this latency leads to progression to gastric cancer needs further study.

Strong shreds of evidence are now emerging on the interaction between *H. pylori* and gastric microbiota as an important factor involved in the etiopathogenesis of gastric cancer. *H. pylori*-induced corpus (body of the stomach)-predominant atrophic gastritis is considered to be the precursor of gastric ulcer and intestinal-type gastric cancer. Corpus-predominant atrophic gastritis increases the gastric pH that leads to altered gastric microbiota, especially increased colonization of stomach by microbes of intestinal origin. Transgenic insulin-gastrin (INS-GAS) germ-free mice when infected with *H. pylori* alone, only 10% of them developed gastrointestinal intraepithelial neoplasia (GIN), while when specific pathogen-free INS-GAS mice were infected with *H. pylori* and complex gastric microbiota, 80% of them developed high-grade and 20% low-grade GIN after 7 months postinfection.[7] Analysis of human gastric microbiota showed the presence of mixed microbial phyla like Firmicutes Actinobacteria, Bacteroidetes, Proteobacteria, and Fusobacteria in decreasing order in *H. pylori*-negative individuals, while gastric microbiota of *H. pylori*-positive subjects were dominated by Proteobacteria. Patients with gastric carcinoma had significantly decreased microbial diversity than patients with chronic gastritis.[8] When gastric microbial dysbiosis index (MDI) was analyzed, it showed that MDI was significantly increased in patients with gastric carcinoma of both Portugal and Chinese cohorts compared to patients with chronic gastritis.[8] MDI was defined as log ratio between total abundance of gastric genera increased and total abundance of gastric genera decreased. Further, the same study also showed that patients with chronic gastritis had Proteobacteria dominated by *H. pylori*, while patients with gastric cancer had Proteobacteria dominated by non-*H. pylori* nitrosating Proteobacteria. Functional analyses showed that nitrosating Proteobacteria were rich in nitrate and nitrite reductases that promoted the production of N-nitroso-compounds and reactive nitrogen species/nitric oxide that likely contributed in gastric carcinogenic. Thus, *H. pylori* acts as a triggering agent of gastric cancer through the induction of corpus-predominant atrophic gastritis with increased gastric pH and altered gastric microbiome dominated by nitrosating bacteria.

Host genetic variability such as IL-1β, TNF-α, IL-8, L-10, and TLR-4 had also been linked to increase the risk of gastric cancer development through enhanced inflammation. Host genes like cyclooxygenase-2 (COX-2; -765G>C) and peroxisome proliferator-activated receptor-gamma (PPAR-γ; Pro12Ala) polymorphisms were investigated among patients with gastric cancer in the presence and absence of *H. pylori* infection. COX-2 C carriers independent of *H. pylori* infection and PPAR-γ G carriers in the presence of *H. pylori* infection were identified as a significant risk for the development of gastric cancer.[9,10] We also observed p53 gene mutation rate of 21% in our gastric cancer patients and this gene mutation was independent of *H. pylori* infection. Thus, host genetic susceptibility also plays an important role in gastric cancer development. Smoking, high salts, and low antioxidant intakes are the other contributing factors in gastric carcinogenesis. Dietary nitrate and nitrite are important nitrosating agents responsible for the generation of N-nitroso-compounds with carcinogenic potentials.

A new era has opened with the discovery of microRNAs (miRNAs), which play an important role in many biological and pathological processes including carcinogenesis. miRNAs are small, noncoding RNAs ~20 to 25 nucleotides in length, which function as critical posttranscriptional regulators of gene expression. Aberrant expression of different miRNAs like miR-21, miR-34a, miR-203, and miR-223 had been reported in gastric cancer.[11] Some miRNAs are upregulated, while others are downregulated in cancerous tissues compared to normal tissues. We observed that *H. pylori* infection influenced the expressions of several miRNAs (unpublished data). The cause and effects of these miRNAs in gastric carcinogenesis in relation to *H. pylori* and its cagPAI need further studies. The role of miRNAs profiling in gastric cancer as diagnostic and prognostic biomarkers calls for further exploration.

In conclusion, despite a close causal link between *H. pylori* infection and the development of gastric cancer, the precise mechanisms involved in this process still remain largely unknown. Studies over the past two decades have revealed that *H. pylori* exert oncogenic effects on gastric mucosa through its complex interaction with bacterial, host, and environmental factors, which calls for further studies.

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