Detecting a Bacterial Protein to Understand Cancer Risk

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In 1982, *Helicobacter pylori* was discovered in the human stomach in association with inflammatory cells infiltrating the gastric mucosa, a condition known as chronic gastritis. Barry Marshall and Robin Warren received the 2005 Nobel Prize in medicine for the discovery of *H. pylori* and determining its role in peptic ulcer disease. Within several years, it became clear that persons carrying *H. pylori* were also at increased risk for the most prevalent types of gastric cancer (1). Yet, *H. pylori* colonization is highly prevalent, and only a fraction of colonized individuals become ill. In my laboratory since 1985 has sought to define the antigens of *H. pylori*, to identify virulence factors, and to develop diagnostic tests to ascertain carriage and genotype. Studies initiated in 1988 by postdoctoral fellow Dr. Timothy Cover focused on an activity in culture supernatants from some but not all *H. pylori* strains that induced vacuole formation in epithelial cells. Cover ultimately purified a protein, which we called VacA, that specifically signals host cells.

In the 1980s, to characterize the vacuolating activity of *H. pylori* strains possessing cagA is associated with an increased risk of developing adenocarcinoma of the stomach. Cancer Res 1995;55:2111–5.4 In July 1989, we purified a clone with a high molecular weight antigen. Dr. Murali Tummuru, another post-doctoral fellow in the lab, completed the cloning and found a 128-kDa protein product (4), which we discovered to be the same protein that Tim Cover studied. We initially called the gene tagA (toxin-associated gene A); however, we learned that Italian colleagues (Antonello Covacci, Rino Rappuoli, and others) had discovered the same protein (5), which they had intended to call caiA (cytotoxin-associated immunodominant gene A). We compromised and coined a single gene name (cagA) that has persisted into the present (4, 5).

Our work and that of Crabtree et al. (2, 3) provided evidence that carrying cagA-positive strains increased the risk of peptic ulcer disease. We then focused on gastric cancer to determine whether cagA positivity was associated with an increased risk for that disease. We used a recombinant fragment (orv660) as an antigen to detect specific serum anti-CagA IgG (6). We validated the assay with serum from persons who were known to be *H. pylori* positive or who were *H. pylori* negative but from whom a cagA-negative strain was isolated. These studies showed a strong specificity for the assay, and nearly all those who had a cagA-positive strain were seropositive (indicating the high sensitivity of the assay).

With Dr. Abraham Nomura, we had previously found an association between *H. pylori* infection and intestinal-type distal gastric cancer in Japanese American men in Hawaii (1). Using the now-validated recombinant CagA assay, we assessed CagA associations with such cancers. Our studies showed that *H. pylori*-positive men who carried a cagA-positive strain had a risk of developing intestinal-type distal gastric adenocarcinoma in the subsequent 21 years that was increased by 130% (odds ratio, 2.3; 95% CI, 1.0–5.2), compared with men carrying a cagA-negative strain (6). Thus, the polymorphisms of *H. pylori* permitted the development of an assay that detects serum responses to a specific bacterial protein and is thereby able to predict the risk for developing the most common form of gastric cancer worldwide.

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4 This article has been cited more than 1012 times since publication.

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Much subsequent work has confirmed our observations, and we now know that *H. pylori* injects the CagA protein into its host’s epithelial cells! The injected CagA interacts with host proteins to determine cell properties and fate. Our work that used host antibody responses detected in clinical samples to probe bacterial antigens has advanced our understanding of gastric carcinogenesis and ultimately opened the door to exploring whether other important clinical conditions are influenced by CagA status.

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**References**


