Anti-CagA Immunoglobulin G Responses Correlate with Interleukin-8 Induction in Human Gastric Mucosal Biopsy Culture

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H. pylori persists in the human stomach despite eliciting both cellular and humoral immune responses and inducing proinflammatory cytokines. To determine whether local humoral and cytokine responses are related to each other and to histologic responses, we studied 66 Japanese patients who underwent gastroscopy. Using specific enzyme-linked immunosorbent assays, we examined gastric antral mucosal-organ biopsy culture supernatants to assess interleukin-6 (IL-6) and interleukin-8 (IL-8) levels and antibody responses to H. pylori whole-cell antigens CagA, HspA, and HspB. Of the patients studied, 11 were H. pylori negative and 55 were H. pylori positive; by PCR, all strains were cagA+. As expected, compared to H. pylori-negative patients, H. pylori-positive patients had significantly higher humoral responses to all H. pylori antigens and had higher IL-8 (47.8 ± 3.5 versus 10.1 ± 4.3 ng/mg of biopsy protein; P < 0.001) and IL-6 levels (2.8 ± 0.3 versus 0.26 ± 0.2 ng/mg of protein; P < 0.001). Among the H. pylori-positive patients, supernatant anti-CagA immunoglobulin G (IgG) levels were significantly associated with H. pylori density (P < 0.005) and neutrophil infiltration (P < 0.005) scores. Anti-CagA immunoglobulin A levels were correlated with intestinal metaplasia (P < 0.05). Mononuclear cell infiltration scores were significantly associated with supernatant IL-6 levels (P < 0.005) and with IgG responses to whole-cell antigens (P < 0.05). Supernatant IL-8 levels were significantly associated with anti-CagA IgG (r = 0.75, P < 0.001). Anti-CagA responses correlated with neutrophil infiltration, intestinal metaplasia, H. pylori density, and IL-8 levels, suggesting that the absolute levels of these antibodies may be markers for gastric inflammation and premalignant changes in individual hosts.

Although essentially all colonized hosts have tissue responses to H. pylori (7, 19, 21), understanding of the mechanisms involved is not well established. Neutrophils may be present in both the epithelial cell layer and underlying lamina propria, and lymphocyte, macrophage, eosinophil, and plasma cell populations in the lamina propria are increased compared to those in H. pylori-negative persons (19). H. pylori produces chemotactic factors that attract neutrophils and mononuclear cells (17, 43, 49) and stimulate the production of chemoattractants from gastric epithelial cells (13, 18).

Among the cytokines present in the gastric mucosa of H. pylori-positive persons, interleukin-8 (IL-8) recruits and activates neutrophils (64), whereas interleukin-6 (IL-6) stimulates lymphocyte and macrophage function (32). Compared with persons not colonized by H. pylori, H. pylori-positive patients have elevated gastric mucosal IL-6 and IL-8 activity, as determined using tissue homogenates and in vitro organ culture (1, 2, 15, 25).

One H. pylori characteristic that has been linked to more intensive tissue responses is the high-molecular-mass (120- to 140-kDa) CagA protein (14, 53). Encoded by cagA (11, 65) and recognized by serum antibodies in persons carrying cagA+ strains (12, 16), serum and mucosal antibodies to CagA are significantly more prevalent among patients with peptic ulceration than among those with gastritis alone (9, 12, 16). Colonization by cagA+ strains induces more intense cellular infiltration in the gastric mucosa (35, 53) and increases the risk of development of atrophic gastritis (5, 37) and gastric cancer (8, 52).

Like other bacteria, H. pylori possesses highly conserved heat-shock proteins (chaperonins) that resemble homologous molecules in human cells (47). Heat-shock protein B (HspB) is a GroEL homolog with a molecular mass of 58 kDa (22, 41), to which virtually all H. pylori-positive persons produce a serum antibody response (55). H. pylori also possesses a GroES homolog (HspA) that has an H. pylori-specific carboxyl terminus. Both hspA and hspB, encoding HspA and HspB, respectively, have been cloned, expressed as fusion proteins with the maltose-binding protein (MBP), and purified in large scale. The MBP-HspA and MBP-HspB fusions are antigenically intact, yet preliminary studies have shown that the MBP-HspA fusion is recognized by sera from only about 40% of H. pylori-positive patients (30, 48, 55, 63).

We sought to determine whether there is a relationship between local gastric humoral immune responses, cytokine production, and histological parameters. To evaluate this association, we examined gastric antral mucosal-organ (biopsy) culture supernatants to assess immunoglobulin A (IgA) and immunoglobulin G (IgG) levels to H. pylori whole-cell antigens (WCA) and CagA, and IgG levels to HspA and HspB, in addition to levels of the cytokines IL-6 and IL-8. We hypothesized that local immune responses might affect the intensity of local cytokine production (as measured by IL-8 and IL-6 levels), reflect the intensity of the mucosal cellular infiltration and the H. pylori density, or both.
MATERIALS AND METHODS

Study groups and biopsies. Sixty-six consecutive patients undergoing diagnos- tic upper gastrointestinal endoscopy (Q20 or Q200; Olympus, Tokyo, Japan) at Nagoya University Hospital were enrolled in this study. The indications for endoscopy in these patients were abdominal pain or discomfort, vomiting, and hematemesis. All endoscopies were done by the same endoscopist. Patients were considered to have duodenal ulcer (DU), gastric ulcer (GU), or no ulcer based on endoscopic findings (Table 1). There was no overlap with the patients in our previous studies (1, 2). The ulcer group was defined as patients having a circumscribed break in the mucosa in the duodenum (i.e., a DU) or in the stomach (i.e., a GU) with apparent depth covered by an exudate, as previously described (3, 53). None of these patients had taken nonsteroidal anti-inflammatory drugs, proton pump inhibitors, antibiotics, or bismuth compounds in the preceding 3 months. At the time of endoscopy, three biopsy specimens were obtained from adjacent areas of the gastric antrum with an Olympus biopsy forceps (FB-24KR [cap size, 6 mm]). When each biopsy specimen was taken, the forceps were fully opened and aimed at right angles to the gastric lumen to the extent possible to obtain uniformly sized biopsies. One biopsy each was used for bacterial culture of

\[ H. pylori \]

routine histological examination (hematoxylin-eosin and immunohistochemical analysis with anti-\( H. pylori \) serum), and in vitro organ culture. Biopsies were obtained from endoscopically intact mucosa distant from focal lesions such as ulcers and erosions. Samples were obtained with informed consent from all subjects in accordance with the Helsinki Declaration.

Assessment of \( H. pylori \) status. The \( H. pylori \) status of patients was determined by bacterial culture, identification of the organism in tissue sections using immuno- histohistochemical analysis, and \( ^{13} \)C urea breath test (UBT) (33). Biopsy spec- imens were homogenized with a glass rod and incubated on brucella 10% new- born calf serum agar plates (BS agar; Intergen) for 5 to 7 days at 37°C in a 5% CO\(_2\) atmosphere. One colony was picked for isolation on a BS agar plate for 3 days. \( H. pylori \) colonies were identified by Gram staining, catalase, oxidase, and urease testing. The UBT was performed with 100 mg of \( ^{13} \)C urea. Breath samples were collected before the test meal was administered and again 20 to 40 min after ingestion of the area. The ratio of \( ^{13} \text{CO}_2 \) to \( ^{12} \text{CO}_2 \) was measured by isotope ratio mass spectrometry, and a 8.1\% CO\(_2\) value of >5 per mil was considered positive for \( H. pylori \). \( H. pylori \) positive patients were defined by positive results in at least two of the diagnostic methods. \( H. pylori \)-negative patients had negative results in all three assays (histology, culture, and UBT) for \( H. pylori \). A chloroform-phenol extraction method was used to obtain DNA from the \( H. pylori \) isolates as previously described (24). Analysis of the presence of \( cagA \) was done by PCR, using primers 5'-GATAAAGCGAAGCAGTTCGTGAAG-3' and 5'-CTGACAAAGTGTTTGCTGAG-3', as previously described (64).

Immunohistochemical analysis for \( H. pylori \) colonization. Antiserum to \( H. pylori \) was raised by injecting formalin-fixed \( H. pylori \) NCTC strain 11637 (5 x 10\(^8\) bacteria) into the auricular vein of a rabbit 10 times every 4 to 6 days. Formalin- fixed biopsy tissues were incubated with a 1:10,000 dilution of the anti-\( H. pylori \) serum, washed, incubated with peroxidase-conjugated goat anti-rabbit immuno- globulins (Dakopatts, Glostrup, Denmark), and developed with 0.03% diamino- benzidine containing 10 mM H\(_2\)O\(_2\). The specificity of this antiserum was con- firmed by absorption with clinical \( H. pylori \) isolates.

Histology. Neutrophil infiltration (activity), mononuclear cell infiltration, glandular atrophy, intestinal metaplasia, and \( H. pylori \) density were assessed on a scale of 0 to 3 corresponding to none, mild, moderate, and severe according to the Sydney System (20, 57), using formalin-fixed biopsy tissues stained with hematoxylin-eosin. All histologic evaluations were performed by one pathologist without knowledge of results from endoscopic diagnosis, \( ^{13} \text{C} \)-labeled UBT, or serological tests.

Gastric biopsy culture. Gastric antral mucosal biopsy tissues were weighed and cultured on a culture insert (Falcon, Oxnard, Calif.) over wells containing RPMI 1640 medium with 5% heat-inactivated fetal calf serum–HEPES buffer–100 U of penicillin G per ml–100 mg of streptomycin per ml (1.0 ml of medium/10 mg of tissue) in a 5% CO\(_2\) incubator for 24 h (38). Biopsies were positioned on the insert with mucosal surfaces up. At the conclusion of the incubation, the culture supernatant was collected from the wells, sterilized by passage through a 0.22-\( \mu \)m-pore-size filter, and stored at −70°C, until assayed for antibody, IL-8, and IL-6 levels. Biopsy tissues were homogenized in 1.0 ml of 3.3 mM CaCl\(_2\), and total protein was assayed by a modified Lowry method (56) to standardize cytokine and antibody results.

IL-8 and IL-6 assays. Levels of IL-8 and IL-6 in the culture supernatant were assayed in duplicate using specific enzyme-linked immunosorbent assays (ELISA) (TFB, Tokyo, Japan) according to the manufacturer’s instructions; the lower limits of detection were 3.0 pg/ml for IL-8 and 4.0 pg/ml for IL-6. The amounts of IL-8 and IL-6 in the organ cultures were expressed as nanograms per milligram of biopsy protein (1, 2).

Detection of antibodies. Assay for \( H. pylori \)-specific IgG and IgA in the biopsy culture supernatants was performed using an ELISA, as previously described (54), with minor modifications. After preliminary checkerboard experiments, a 1:25 dilution was found to be the optimal dilution for subsequent antibody assays. Culture supernatants were diluted 1:25 in phosphate-buffered saline (PBS), incubated 1 h in a microtiter plate well containing 1.0 \( \mu \)g of sonicated pooled \( H. pylori \) WCA prepared as previously described (51, 54). Goat anti-human IgG and IgA were used at 1:4,000 and 1:2,000 dilutions, respectively. Color was devel- oped, and optical densities were read as previously described (54). ELISA to detect anti-CagA IgG and IgA was performed using recombinant CagA antigen as previously described (8), with minor modifications. Culture supernatants were diluted 1:25 in PBS, incubated 1 h in a microtiter plate well containing 250 ng of recombinant CagA, and subsequently incubated with goat anti-human IgG (1: 4,000) or goat anti-human IgA (1:2,000). The results for each sample are ex- pressed as the ratio of the optical density (ODR) value of the sample to the four positive control sera (51), and normalized for biopsy protein (ODR per milli- gram of protein). Antibody responses to HspA and HspB of \( H. pylori \) were measured as previously described (55). In brief, antigen was purified from \( E. coli \) strain M1001 expressing HspA or HspB as a fusion protein with MBP (HspA-MBP or HspB-MBP) using large-scale amylose affinity. Purified MBP alone was used as a control antigen. For both fusion proteins, the optimal antigen concentration was 125 ng/ml, and MBP alone was used at a concentra- tion of 62.5 ng/ml, as previously described. Culture supernatants were di- luted 1:20 in PBS and incubated 1 h, and goat anti-human IgG was used at 1:4,000.

Statistical analysis. Statistical analysis was performed by \( \chi^2 \), Fisher’s exact, paired-\( t \)-, or Mann-Whitney U tests, depending on the characteristics of the data set of concern. Variables with a \( P \) value of <0.15 on bivariate analysis were entered into a multivariate logistic regression model. A \( P \) value of <0.05 was considered statistically significant.

RESULTS

Assessment of \( H. pylori \) and \( cagA \) status of the study sub- jects. In total, 66 patients were studied; 37 (67%) were male. Of the 66 patients, 55 (84%) were found to be \( H. pylori \) positive (Table 1). By definition, patients were defined as \( H. pylori \) positive if at least two diagnostic assays were positive. The sensitivity for \( H. pylori \) detection for UBT was 100%; that for histology was 94.3%, and that for bacterial culture was 92.5%. Of the 55 \( H. pylori \)-positive patients, 38 had peptic ulcer dis-
case (GU, 14; DU, 24). All *H. pylori* isolates were found to be *cagA*+ by PCR. Each of the 11 *H. pylori*-negative patients had nonulcer dyspepsia (NUD). There were no clinical findings consistent with the presence of *H. pylori*.

**Histological findings.** We first compared the intensity of antral histological findings (infiltration with mononuclear or polymorphonuclear cells, atrophy, and metaplasia) among *H. pylori*-positive and -negative patients (Table 1). The *H. pylori*-positive patients showed significantly higher scores than did the *H. pylori*-negative patients for all four histological features (Table 1). The 24 patients with DU disease had significantly higher mononuclear and polymorphonuclear cell infiltration scores than did the 17 patients with NUD. GU patients had higher atrophy and metaplasia scores than either DU or NUD patients and higher scores for mononuclear cell infiltration than NUD patients. No significant differences in mononuclear cell infiltration were observed between DU and GU patients.

**Gastric biopsy culture antibody levels.** Next we examined the levels of antibodies present in the gastric biopsy culture supernatants from this same group of patients. As expected, all antibody responses to *H. pylori* antigens were significantly higher in *H. pylori*-positive patients than in *H. pylori*-negative patients (Table 2). However, there were no significant differences in any of the measured levels of antibodies in culture supernatants among *H. pylori*-positive patients with differing endoscopic diagnoses.

**Cytokine production.** We next determined whether IL-6 and *C. pylori* culture supernatant levels of IgG to *H. pylori* antigens were associated with increased IL-8 density. Levels of gastric biopsy culture in 66 Japanese patients, by patient *H. pylori* status and endoscopic findings

<table>
<thead>
<tr>
<th>Endoscopic finding</th>
<th>No. of patients</th>
<th>Level of antibody to*</th>
<th>WCA</th>
<th>CagA</th>
<th>HspA (IgG)</th>
<th>HspB (IgG)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H. pylori-positive cases</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DU</td>
<td>24</td>
<td>1.55 ± 1.84</td>
<td>0.36 ± 0.28</td>
<td>0.36 ± 0.28</td>
<td>0.08 ± 0.25</td>
<td>0.22 ± 0.46</td>
</tr>
<tr>
<td>GU</td>
<td>14</td>
<td>1.69 ± 2.90</td>
<td>0.23 ± 0.26</td>
<td>0.23 ± 0.26</td>
<td>0.18 ± 0.58</td>
<td>0.20 ± 0.40</td>
</tr>
<tr>
<td>Nonulcer</td>
<td>17</td>
<td>0.75 ± 2.59</td>
<td>0.20 ± 0.28</td>
<td>0.20 ± 0.28</td>
<td>0.04 ± 0.12</td>
<td>0.23 ± 0.87</td>
</tr>
<tr>
<td>All</td>
<td>55</td>
<td>1.34 ± 2.37</td>
<td>0.28 ± 0.28</td>
<td>0.28 ± 0.28</td>
<td>0.10 ± 0.34</td>
<td>0.22 ± 0.59</td>
</tr>
<tr>
<td>H. pylori-negative cases</td>
<td>11</td>
<td>0.003 ± 0.008</td>
<td>0.002 ± 0.003</td>
<td>0.015 ± 0.014</td>
<td>0.001 ± 0.003</td>
<td>0.000 ± 0.001</td>
</tr>
</tbody>
</table>

* Antibody levels are shown as mean ± standard deviations of ODR per milligram of protein units for anti-WCA IgG and IgA and anti-CagA IgG and IgA assays and as mean ± standard deviations of net optical density for the anti-HspA and anti-HspB assays.

* As shown in Table 1. For all values, P < 0.05 compared with the 55 *H. pylori*-positive cases.

**Correlations with immunological scores.** We asked whether, among the 55 *H. pylori*-positive patients, there was any relationship between biopsy culture supernatant antibody, cytokine levels, and histological findings. Culture supernatant IL-8 levels were strongly correlated (r = 0.75; P < 0.001) with levels of anti-CagA IgG (Fig. 2) but not with anti-CagA IgA, anti-WCA IgE, or IgA antibodies (data not shown). Culture supernatant IL-6 levels were not significantly correlated with levels of either IgA or IgG anti-CagA antibodies. There were no significant correlations between gastric biopsy culture supernatant cytokine levels and antibodies directed to *H. pylori* WCA, HspA, or HspB (data not shown).

We next examined whether cytokine and antibody levels were predictive of histologic findings. We categorized age and levels of IL-8, IL-6, anti-WCA IgG, anti-WCA IgA, anti-CagA IgG, and anti-CagA IgA by quartiles. Dichotomous outcome variables for mononuclear cell infiltration, neutrophil infiltration, atrophy, and *H. pylori* density were grouped as high (Sydney scale score, 2 or 3) or low (Sydney scale score, 0 or 1). Metaplasia was categorized as present (Sydney scale score, 1 to 3) or absent (Sydney scale score, 0). Multivariate analysis revealed several significant associations (Table 3). Female gender had an independent protective effect, with females having a significantly lower rate of neutrophil infiltration and *H. pylori* density than males. Older age correlated with a greater risk of gastric atrophy, and the risk increased linearly by quartile. Although levels of biopsy culture supernatant IL-8 did not predict histologic findings, high IL-6 levels were independent predictors of mononuclear cell infiltration, as were high biopsy culture supernatant levels of IgG to *H. pylori* WCA. Levels of gastric biopsy culture supernatant IgG antibodies to CagA were independently associated with increased neutrophil infiltration and *H. pylori* density. Levels of gastric biopsy culture supernatant IgA antibodies to CagA were associated with increased risk of metaplasia.

**DISCUSSION**

Humans colonized with *H. pylori* show a variety of responses to the organisms in their gastric tissues (6, 35, 44). The response can be considered to have an “acute inflammatory” component, characterized by intraepithelial and interstitial infiltration by polymorphonuclear leukocytes, and a “chronic inflammatory” component associated with increased numbers of mononuclear cells, including lymphocytes, monocytes/macrophages, and plasma cells in the lamina propria (19). However, among *H. pylori*-positive human populations, there is...
substantial heterogeneity in the intensity and distribution of these histological responses (59). The basis of this heterogeneity and its relation to clinical diagnoses represent important unsolved questions (6, 19).

The cytokines induced by *H. pylori* colonization, including tumor necrosis factor alpha, interleukin-1 (IL-1), IL-6, and IL-8, may play roles in regulating these tissue responses (1, 2, 15, 25, 50). IL-8 has been implicated in the pathogenesis of infectious and inflammatory conditions associated with neutrophil infiltration (34, 42, 60), whereas IL-6 may be involved in inflammation through its broad effects on growth, differentiation, and activation of mononuclear cells, including T- and B-lymphocytes and macrophages (26, 27, 38, 40), through the induction of other cytokines such as monocyte chemoattractant protein 1 (10).

In this study, as expected, in comparison with *H. pylori*-negative patients, *H. pylori*-positive patients had higher scores for mononuclear and polymorphonuclear cell infiltration, IL-8 and IL-6 levels, and *H. pylori*-specific antibodies in the gastric biopsy culture supernatants (1, 2, 15, 25). By multivariate analyses, we found that mucosal IL-6 but not IL-8 levels correlated with both mononuclear cell infiltration scores, and this is consistent with the prior literature (2, 65). We have previously reported that, in biopsy specimens from persons colonized with *H. pylori*, IL-8 mainly is present in gastric epithelial cells and macrophages (2), and IL-6 is present chiefly in macrophages (1). The absence of a correlation with IL-8 levels in multivariate analysis suggests that this cytokine does not exert an independent effect on histological change, and IL-8 may be chiefly produced by epithelial cells, which is consistent with other reports (13, 18). Compared to levels in patients with NUD, significantly elevated antral IL-8 and IL-6 levels were found in patients with DU, suggesting that the altered gastric secretory pathophysiology in DU patients (36, 45, 67) may be driven at least in part by these cytokines. These results are consistent with previous observations (4, 58) that DU patients

![Diagram](http://cvi.asm.org/)

**FIG. 1.** Cytokine levels (nanograms per milligram of protein in culture supernatants) in gastric antral mucosal-organ cultures from 66 study patients. Patients were classified based on *H. pylori* status and, if positive, on endoscopic findings. (A) IL-8. Values for *H. pylori*-positive persons in each group were significantly (*P* < 0.001) higher than for *H. pylori*-negative persons. Patients with DU had the highest values. (B) IL-6. Values for *H. pylori*-positive persons in each group were significantly (*P* < 0.001) higher than for *H. pylori*-negative persons.

![Diagram](http://cvi.asm.org/)

**FIG. 2.** Correlation between organ culture IL-8 levels and concentrations of IgG to CagA in 55 persons colonized with *cagA*+ *H. pylori* strains (*r* = 0.75, *P* < 0.0001).
have substantial infiltration with polymorphonuclear cells in gastric or duodenal mucosa. The elevated IL-6 levels in DU patients compared with NUD patients are consistent with differences in antral mononuclear cell scores (Table 1) and suggest potential mechanisms for the altered pathophysiology in DU patients. Patients with DU disease had significantly higher mononuclear and polymorphonuclear cell infiltration scores than did patients with NUD, whereas GU patients had higher atrophy and metaplasia scores than either DU or NUD patients and higher scores for mononuclear cell infiltration than NUD patients. These findings confirm that DU patients have more severe antral gastritis, and GU patients tend to have gastric atrophy, supporting previous work showing different H. pylori colonization patterns in DU and GU patients in relation to acid production and the presence of atrophy (39).

IL-8 induction is H. pylori strain specific in that, on average, cagA-positive strains induce higher levels (13, 53, 61, 66, 69) than do cagA-negative strains. That all of our tested 55 strains were cagA-positive is consistent with previous studies of Japanese H. pylori-positive patients (28, 46). Despite the universal presence of cagA strains, considerable variation of gastric biopsy culture supernatant IL-8 and IL-6 activity was present among individual H. pylori-positive patients, and importantly, the levels of IL-8 were strongly correlated with levels of anti-CagA IgG. The mechanisms underlying this association are not known, and this observation should be confirmed in other populations. Since H. pylori density also was significantly correlated with anti-CagA antibody, we hypothesize that the correlation between IL-8 and anti-CagA antibodies may reflect the local inflammatory response, which is dependent on the density of H. pylori. This is supported by our finding that H. pylori density is significantly correlated with anti-CagA IgG in gastric biopsy supernatant. Similarly, the specific antibody levels may reflect the intensity of the interaction of the H. pylori population with the host. Carriage of CagA-positive H. pylori strains has been associated with an increased prevalence and intensity of antral atrophy and intestinal metaplasia, in addition to higher degrees of cellular infiltration in gastric tissues (23, 37, 62, 68). The significant correlation between levels of anti-CagA IgA in organ culture supernatants and metaplasia scores could be due to a direct toxic effect by the antibodies or could reflect a more intense colonization by the particular strains in these patients or represent a phenomenon secondary to the metaplasia. That serum anti-CagA IgG levels vary in relation to variation of the 3' region of cagA (70) might provide an intermediary mechanism for our observation concerning organ culture supernatant antibody levels. Regardless of the mechanisms involved, that anti-CagA antibody responses were correlated with IL-8 levels and intestinal metaplasia indicates their possible role as markers of gastric inflammation and premalignant lesions. Bacterial Hsps may play an important role in inflammation (71), and human Hsp60 and H. pylori HspB have antigenic similarities (31). An Hsp60 epitope is detected on the surface of both human gastric cancer cells and human gastric biopsy specimens, and the intensity of cell surface Hsp60 correlated significantly with adhesion of H. pylori to human gastric cancer cells (29). Although we found that, as expected, levels of antibodies to HspA and HspB in the gastric biopsy culture supernatants were higher in H. pylori-positive than -negative patients, the lack of correlation between the particular levels and the histological findings suggests that these proteins may not be relevant to the induction of the specific patterns of gastric mucosal tissue responses related to disease outcome.

In conclusion, these findings indicate that quantitative evaluation of antibodies and cytokines in gastric antral biopsy culture supernatant, as well as histological scores, provides a means for examining individual variations in host responses to H. pylori. Such analyses can both raise and address hypotheses concerning the relationships between colonization and clinical outcomes. That anti-CagA responses correlated with intestinal metaplasia, H. pylori density, and IL-8 suggests that the absolute levels of these antibodies may be markers for gastric inflammation and premalignant changes in individual hosts.

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