Differential Stimulation of Interleukin-12 (IL-12) and IL-10 by Live and Killed Helicobacter pylori In Vitro and Association of IL-12 Production with Gamma Interferon-Producing T Cells in the Human Gastric Mucosa


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The objective of these experiments was to examine the ability of Helicobacter pylori to stimulate interleukin-10 (IL-10) or IL-12 and select for either Th1 or Th2 cells. Gastric biopsy specimens were collected from patients who were categorized with respect to the presence of H. pylori and gastric disease as well as their age, gender, medications, and other factors. As Th1 and Th2 cells are selected by IL-12 and IL-10, respectively, biopsy specimens were screened for mRNA and protein for these cytokines. Although mRNA for IL-12 and IL-10 was detected in biopsy specimens obtained from both infected and uninfected patients, IL-12 protein predominated. Levels of IL-10 and IL-12 in gastric tissue did not change in response to infection. Moreover, gamma interferon (IFN-γ)-producing T cells were found in both the infected and the uninfected gastric mucosa. Stimulation of peripheral blood leukocytes from either infected or uninfected donors with various concentrations of live or killed H. pylori induced immunoreactive IL-12 and IL-10. After stimulation with live H. pylori, IL-12 levels increased more than 30-fold, whereas IL-10 levels increased only 2- to 5-fold, compared to cells stimulated with medium alone. Interestingly, killed H. pylori induced significantly more IL-10 (P < 0.05) than live H. pylori, while recombinant urease only induced IL-10. These results demonstrate that live H. pylori selectively stimulates the induction of IL-12 and Th1 cells that produce IFN-γ, whereas preparations used in oral vaccines induce more IL-10 and may favor Th2 cell responses.

Helicobacter pylori infects a substantial proportion of the population, and this infection leads to the development of chronic, active gastritis (16, 20, 26). In a relatively small portion of infected individuals, H. pylori contributes to the development of more severe gastric pathology including peptic ulceration and gastric cancer (3, 7). Investigations have shown that family members can express different manifestations of gastric disease even though they are infected with genetically similar strains of H. pylori (1a, 2). This, and other evidence, suggests that virulence factors of H. pylori interact with other elements within the gastric milieu to cause the more severe gastric diseases observed in some infected patients. Since the gastric mucosa is infiltrated with immune and inflammatory cells during H. pylori infection, the host response may represent one element that contributes to the pathogenesis of disease associated with H. pylori infection.

It is generally believed that immunoglobulin A (IgA) contributes substantially to effective immunity in the mucosal tissues, including the gastrointestinal tract. Moreover, this isotype is selected by cytokines secreted by the Th2 subset of helper T cells including interleukin-4 (IL-4), IL-5, IL-6, and transforming growth factor β (35, 37, 45, 55, 59, 62). The inability of the host to clear the H. pylori infection suggests that the local immune responses are not quantitatively or qualitatively adequate. Thus, one might predict that Th1 responses predominate during persistent infection with H. pylori. In fact, H. pylori has been shown to stimulate the production of gamma interferon (IFN-γ) by peripheral blood mononuclear cells (PBMC) (56). Other studies have shown that gastric mononuclear cells isolated from infected patients produce IFN-γ (21, 34) while IL-4-producing cells are relatively infrequent in these preparations (34). More recently, T-cell clones have been derived from infected patients, and most are characterized as being Th1-like (15). These observations support the notion that H. pylori preferentially induces the expansion of Th1 cells.

Helper T-cell subset selection is mediated at least in part by cytokines. In particular, IL-12 and IL-10 production have been implicated in the selection of Th1 and Th2 cells, respectively (24, 43, 52). Thus, the purpose of this study was to evaluate the relative expression of IL-12 and IL-10 in gastric mucosa and to determine the relative numbers of IFN-γ and IL-4-producing T cells in this tissue. The data presented suggest that IL-12 does predominate in the gastric tissue and that stimulation with live H. pylori leads to IL-12 production and selection of Th1 cells. The implications for this concerning gastric immunity to H. pylori are discussed.

MATERIALS AND METHODS

Patient population. Tissue and blood used for these studies were obtained from consenting adults (20 to 55 years old) as approved by the institutional review boards at Baylor College of Medicine and the University of Texas Medical Branch. Biopsy specimens of the gastric antrum were obtained from consenting adults (20 to 55 years old) as approved by the institutional review boards at Baylor College of Medicine and the University of Texas Medical Branch. Biopsy specimens of the gastric antrum were obtained from consenting adults (20 to 55 years old) as approved by the institutional review boards at Baylor College of Medicine and the University of Texas Medical Branch.
patients undergoing esophago-gastro-duodenoscopy for various clinical indications. These subjects were considered to be infected if _H. pylori_ was detected by either a rapid urease test or histopathology of the biopsy specimens. Individuals regularly using nonsteroidal anti-inflammatory drugs or antisyecretory drugs were excluded from the study population. All of the infected patients selected as the source of biopsy specimens were diagnosed with gastritis that was not complicated with peptic ulcer or gastric cancer. Control tissue from uninfected patients did not have any evidence of gastritis or ulceration. PMBC were isolated from a separate group of infected (but asymptomatic) and uninfected volunteer donors. The status of infection with _H. pylori_ in these donors was determined by serology, with ELISA kits kindly provided by BioWhitarcck (Walkervilse, Md.), as described previously (53). PMBC were isolated from heparinized venous blood of _H. pylori_-infected and uninfected donors with Ficoll-Hypaque density gradients by standard techniques (13, 14). Cells were washed in RPMI 1640 (GIBCO, Grand Island, N.Y.) without antibiotics but containing 1-glutamine and 10% heat-inactivated fetal calf serum (FCS) (Intergen, Purchase, N.Y.) and were counted, and viability was ascertained by trypan blue exclusion.

Gastric T cells were isolated by a modification of previously described techniques (2a, 21). Briefly, biopsy specimens were collected into collection medium at 4°C (calcium- and magnesium-free Hanks balanced salt solution with 5% FCS and penicillin plus streptomycin). The biopsy specimens were stored at 4°C for up to 18 h prior to processing, this having previously been shown not to alter T-cell function. All manipulations were carried out by using aseptic techniques. Biopsy specimens were rinsed with aqueous betadine and then immediately grown in 24-well plates and were stimulated with medium alone or with various preparations. These subjects were considered to be infected if _H. pylori_ 4230.

CO2, 5% O2, and 85% N2). The concentration of the bacteria was estimated by measuring the absorbance of the suspension and comparing the value to a growth curve. Incubation (37°C, 5% CO2) for 18 h, supernatants were collected, filtered, and the bacteria were cultured by inoculation into 10 ml of brucella broth (GIBCO) supplemented with 10% and 30-kDa polypeptides. Subsequently, the material was stored at 4°C (calcium- and magnesium-free Hanks balanced salt solution with 5% FCS and penicillin plus streptomycin). The biopsy specimens were stored at 4°C for up to 18 h prior to processing, this having previously been shown not to alter T-cell function. All manipulations were carried out by using aseptic techniques. Biopsy specimens were rinsed with aqueous betadine and then immediately grown in 24-well plates and were stimulated with medium alone or with various preparations. These subjects were considered to be infected if _H. pylori_ 4230.

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free of microscopic gastritis. The tissue was sonicated in the presence of buffers and protease inhibitors before being assayed for IL-12 and IL-10 by radioimmunoassay or enzyme-linked immunosorbent assay. Whereas IL-10 was virtually undetectable, IL-12 was detected in samples from both infected and uninfected tissue (Fig. 1). No statistically significant difference between the levels of either cytokine was observed in the tissues obtained from the infected and uninfected donors. The low levels of IL-10 were unlikely to be due to adsorption or degradation of the IL-10 as IL-10 could be detected in biopsy material after spiking the samples with exogenous, recombinant human IL-10.

Expression of IL-12 and IL-10 mRNA in gastric biopsy specimens. To evaluate the association between mRNA and protein in the gastric tissue, RNA was extracted from gastric biopsy specimens, reverse transcribed, and amplified by PCR with primers for IL-10, IL-12, and β-actin. After performing reverse transcription-PCR, the PCR products were transferred to membranes and assayed by Southern blotting. The presence of β-actin product in all samples verified the integrity of the mRNA (data not shown). In general, the amount of mRNA for IL-12 p40 varied although it was more easily detected in the infected specimens (Fig. 2). In general, mRNA levels for IL-10 were lower in infected than in uninfected patients. The range of expression of mRNA resembled the variation in our ability to detect immunoreactive IL-10 and IL-12 proteins as shown in Fig. 1.

Preferential production of IFN-γ by gastric T cells. In view of the evidence that IL-12 was detected in gastric biopsy specimens at significantly higher levels than IL-10, mononuclear cells were isolated from biopsy specimens, activated for 4 h, stained for CD3 to identify them as T cells, and then examined for the expression of intracellular IFN-γ or IL-4. IFN-γ could be detected in CD3+ T cells isolated from the gastric mucosa of both infected (mean ± SEM percent positive for four subjects, 85.6% ± 12.7%) and uninfected subjects (mean ± SEM percent positive for four subjects, 63.8% ± 21.5%). In contrast, less than 5% of the CD3+ T cells were shown to produce IL-4 (data not shown). These results suggest that the relative predominance of IL-12 in both infected and uninfected gastric tissue is associated with Th1-like cells.

Induction of IL-12 by H. pylori. Since Th1 cells predominate in both uninfected and infected gastric tissue, the ability of H. pylori to induce IL-12 was examined. Given the difficulty of isolating sufficient numbers of mononuclear cells from biopsy specimens for in vitro culture, PBMC from infected or uninfected donors were stimulated with 10^6 bacteria/ml of live or killed H. pylori for 18 h. This concentration was previously determined to induce both IL-10 and IL-12. SAC (1:10,000 [vol:vol]) and LPS (1 μg/ml) were used as positive controls (36). Subsequently, supernatants were collected and assayed for immunoreactive IL-12 by radioimmunoassay. Live H. pylori induced a greater IL-12 response (P < 0.05) than the positive-control cultures or the cultures stimulated with killed bacteria (Fig. 3).

The effect of H. pylori concentration on cytokine secretion. PBMC from infected or uninfected donors were stimulated with increasing numbers of live H. pylori ranging from 10 to 1 × 10^7 bacteria/ml. After 18 h, the supernatant was collected, and the concentrations of IL-10 and IL-12 were determined. As
shown in Fig. 4, the concentrations of both cytokines increased as the concentration of *H. pylori* increased. Whereas the increase in IL-10 was approximately 5-fold more than the level in control supernatants from cells in medium alone, the concentration of IL-12 increased over 30-fold, from a mean of 30 pg/ml in control supernatants to 1,007 pg/ml, in response to stimulation with 10⁷ organisms/ml.

Influence of the immune status on the cytokine response. In order to determine if prior natural exposure to *H. pylori* altered the immune status of the host and affected the detection of IL-12 and IL-10, the cytokine responses of PBMC from seropositive and seronegative donors were compared for a range of doses of *H. pylori*. PBMC from uninfected (n = 6) and infected patients (n = 6) were exposed to 10⁶ bacteria/ml, and the supernatants were collected and assayed. No statistically significant differences in IL-12 or IL-10 production were observed when the seropositive and seronegative groups were compared (Fig. 5).

Comparison of different preparations of *H. pylori* on cytokine production. Previous studies have suggested that persistent infection of mice with *Helicobacter* spp. is associated with Th1-cell responses (47), while mice can be made immune by oral vaccine preparations that favor the induction of a Th2-cell response (5, 12). These vaccines have employed killed, whole-cell preparations of *H. pylori* (38) or recombinant *H. pylori* urease (11, 22, 40, 46, 50). As live bacteria, killed bacteria, and bacterial subunits are known to vary in their ability to direct the differentiation of T cells, we compared the relative production of IL-12 and IL-10 using killed *H. pylori*, live *H. pylori*, and 1.0 µg of recombinant urease/ml. All three stimuli differed significantly in their ability to induce IL-12 and IL-10. Both live and killed *H. pylori* caused a statistically significant increase in the IL-10 concentration over the basal level. In addition, killed *H. pylori* induced a fourfold increase in IL-10 that was significantly greater than the twofold increase induced by live organisms (P < 0.05) (Fig. 6). In contrast, live *H. pylori* induced significantly more IL-12 compared to killed organisms (P < 0.05). The differential abilities of the live and killed bacterial preparations to induce either cytokine were also evident when the relative ratios of IL-12 and IL-10 were compared. The ratio of IL-10 to IL-12 was 1.4:1 after stimulation with live *H. pylori* in contrast to a ratio of 3.9:1 after stimulation with killed bacteria. Urease alone induced a significant IL-10 response but did not induce an IL-12 response.

DISCUSSION

Previous studies have shown that *H. pylori* is capable of inducing the production of IFN-γ (56). Recent reports have
The presence of mRNA and immunoreactive protein for IL-12 in both infected and uninfected gastric tissue suggests that the stomach favors the selection of the Th1 subset of T cells. This notion is supported by the observation that IFN-\(\gamma\)-producing T cells predominated in the gastric mucosa of both infected and uninfected subjects. However, the total number of the Th1-like cells increases during infection (2a). Moreover, a marked increase in the absolute number of IFN-\(\gamma\)-producing cells has been described in both bacterial and noninfectious gastritis (34). These data suggest that Th1 cells predominate in the normal gastric mucosa as well as during inflammation including gastritis associated with \textit{H. pylori} infection.

The variation in the expression of mRNA for IL-12 and IL-10 in gastric tissue was substantial and may have contributed to our inability to identify a statistically significant difference between the levels of immunoreactive protein in infected and uninfected individuals. Moreover, it is possible that higher levels of these cytokines will be detected in patients infected with specific strains of \textit{H. pylori} or in patients with different gastric diseases when these parameters are compared to the results from tissue in which gastritis was the only clinical manifestation of the infection. Despite the variation in the levels of IL-10 mRNA, the gastric tissue had relatively low levels of IL-10. Biologically significant changes in the expression of this cytokine may have been lost by the dilution of the biopsy specimens. Alternatively, selective sampling may obscure important changes in expression associated with infection that may be detectable by histochemical techniques. However, levels of IL-10 and IL-12 in the corpus of the stomach correlated well to those in the antrum of the same patient although the levels in the corpus were generally lower (unpublished observations). Thus, the results suggest that IL-12 does indeed predominate in gastric tissue and may correlate to the predomination of Th1 cells.

Since gastric mononuclear cells are not easily isolated in numbers that permit extensive manipulation in vitro, PBMC were used to examine the ability of \textit{H. pylori} to stimulate cytokine responses. Live \textit{H. pylori} was shown to induce a substantial production of the p40 chain of IL-12 by PBMC. In fact, the response to a range of doses of \textit{H. pylori} was equal to or greater than the response to the positive controls, LPS and SAC. Since these studies were performed using PBMC, it is possible that the response differs from what might be observed in the gastric mucosa. This is evidenced by the fact that \textit{H. pylori} induced IL-10 in PBMC but the concentration of this cytokine was extremely low in gastric tissue. Moreover, \textit{H. pylori} is noninvasive so most responses by cells in the gastric lamina propria are probably driven by soluble material that has crossed the epithelial barrier. Thus, it will be important to characterize the cells responsible for the production of IL-12 in gastric mucosa as well as the response of these cells to soluble factors released by \textit{H. pylori}. These difficulties notwithstanding, it appears as if IL-12 is present in both infected and uninfected tissue and can play a role in regulating the gastric immune response.

Biologically active IL-12 is a heterodimer of 70 kDa composed of p35 and p40 subunits (57). The p40 subunit is virtually always produced in levels that exceed those of p70, and therefore, measuring levels of p40 does not directly predict the induction of IL-12 bioactivity. It has been suggested that monomers and homodimers of p40 may act as antagonists for IL-12 in vitro with murine (44) and human systems (41). However, the role of IL-12 p40 as a significant antagonist in vivo is unlikely as the p35 subunit is essential for optimal receptor binding (41).

Whereas stimulation of monocytes by LPS alone preferentially induces IL-12 p40, priming of monocytes and macrophages with IFN-\(\gamma\) and/or tumor necrosis factor alpha (TNF-\(\alpha\)) can stimulate the transcription of both p40 and p35 (42), leading to the production of biologically active IL-12 after exposure to LPS (4, 32) or mycobacterial infection (25). Moreover, IFN-\(\gamma\) has stronger effects on the production of biologically active IL-12 than on the induction of p40 due to its ability to preferentially enhance the production of IL-12 p35 (54). Since TNF-\(\alpha\) expression is increased during infection (9) and gastric T cells appear to be of the Th1 type, inflammatory material from \textit{H. pylori} as well as TNF-\(\alpha\) and IFN-\(\gamma\) are usually present together and would facilitate the production of biologically active IL-12. This is supported by an earlier study by Tarkkanen et al. showing that \textit{H. pylori} is capable of inducing IFN-\(\gamma\) and enhancing NK cell activity in PBMC (56). As biologically active IL-12 was previously referred to as natural killer cell stimulatory factor (43), it is likely that the results presented by Tarkkanen and colleagues reflect the ability of \textit{H. pylori} to stimulate the production of biologically active IL-12, which ability led to their observed increase in IFN-\(\gamma\) and NK cell activity.

These models assume that IL-12 selects for Th1 cells, but recent studies show that IL-12 can induce both IL-4 and IL-10 production (28, 33, 61). This suggests that IL-12 may combine with other stimuli to select for a particular T-cell phenotype. However, in some of these systems, IL-12 was working directly on T-cell clones and in others it was working in the presence of other modulators such as anti-IL-4 (61). Moreover, one of the major \textit{H. pylori} cellular proteins, urease, induced IL-10 independent of IL-12. Thus, while IL-12 may have contributed to IL-10 production in some studies, in the system described in this report, IL-12 levels were inversely correlated to those of IL-10 in both the in vitro cultures and the gastric tissue.

Further evidence that persistent infection with \textit{Helicobacter} \textit{spp.} is associated with a Th1 response is found in animal models. Several investigators have shown that \textit{Helicobacter felis} can persistently infect the stomachs of mice (39), and this is associated with a Th1 response (47). The presence of Th1 cells and IFN-\(\gamma\) would be consistent with the marked increase in major histocompatibility complex class II molecules that are expressed on gastric epithelial cells in the inflamed stomach during \textit{H. pylori} infection (6, 58). These gastric Th1 cells may favor the destruction of tissue through cell-mediated immune responses rather than the eradication of this extracellular pathogen (20). The absence of potentially anti-inflammatory cytokines from Th2 cells may prevent the Th1 responses from being restrained. In addition, Th1 cells could enhance the production of complement-fixing antibodies in the gastric tissue. In view of the reports that antibodies produced in response to \textit{H. pylori} can bind to cells within the gastric mucosa and contribute to gastric inflammation (1, 30, 48, 60), gastric damage may be enhanced further by the inappropriate regulation of local B-cell responses by Th1 cells.

In contrast to natural infection, administration of oral vaccines and adjuvants, such as cholera toxin or \textit{E. coli} labile toxin,
that select for a relatively greater Th2 response can clear and prevent infection with H. felis (5, 8, 11, 12, 18, 23, 38, 51). Other investigators have shown that these vaccine preparations are also effective at clearing an existing infection (17), possibly by inducing additional, complementary Th2-cell responses. Thus, the selection of the appropriate antigen and adjuvant may facilitate the induction of a response that differs substantially from that induced by natural infection with live H. pylori. The fact that killed H. pylori and urease alone induced relatively more IL-10 than live H. pylori supports the notion that vaccines, including whole-cell vaccines and recombinant urease, may be effective due to their ability to alter the selection of T-cell subsets.

In summary, the data presented in this report support the view that the relative expression of IL-10 and IL-12 in the human immune response favors the development of a subset of helper T cells that are biased to IFN-γ production. In turn, this response is associated with Th1 cells and enhanced cell-mediated immunity. Additional studies are in progress to further define the functional properties of gastric T cells in response to H. pylori infections.

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