Expression of Interleukin-18, a Th1 Cytokine, in Human Gastric Mucosa Is Increased in Helicobacter pylori Infection

Toshikoto Tomita, Andrew M. Jackson, Nobuyuki Hida, Mumtaz Hayat, Michael F. Dixon, Takashi Shimoyama, Anthony T. R. Axon, Philip A. Robinson, and Jean E. Crabtree

Helicobacter pylori (H. pylori), a campylobacter-like organism, infects the stomach mucosa of almost half of the world’s population, causing gastritis, peptic ulcer disease, and gastric adenocarcinoma. H. pylori is the most common bacterial infection in the world, affecting over 50% of the global population. The infection is acquired early in life and is associated with a high risk of developing gastric cancer. H. pylori infection is characterized by chronic inflammation of the stomach, which may progress to peptic ulcer disease and gastritis. The pathogenesis of H. pylori infection is complex and involves both bacterial and host factors. The immune response to H. pylori is a major factor contributing to gastric mucosal damage. Chronic infection with H. pylori is associated with interferon-γ-producing T cells and increased mucosal IL-12, indicative of a predominant Th1 response. IL-12 mRNA expansion levels are increased in infection with H. pylori, indicative of a predominant Th1 response. IL-12 mRNA expansion levels are increased in infection with H. pylori, indicative of a predominant Th1 response.

Interleukin-18 (IL-18) is a recently identified cytokine (originally termed interferon-γ-inducing factor) that was cloned from the liver of lipopolysaccharide-challenged mice infected with Propionibacterium acnes. IL-18 is related to the IL-1 family of cytokines and is expressed by various cell types, including immune cells and epithelial cells. IL-18 is synthesized as a biologically inactive 24-kDa precursor protein, which is cleaved to the active 18-kDa form by caspase-1, the enzyme involved in the processing of pro-inflammatory cytokines. The processing of IL-18 by active caspase-1 is essential for the biologic effects of IL-18.

IL-18 has an important role in defense against pathogens, by stimulating innate defenses and promoting Th1 responses. IL-18 enhances NK cell cytotoxicity and is synergistic with IFN-γ in potentiating both interferon-γ production and NK cell cytotoxicity. Many of the cellular responses of IL-18 are similar to the biologic functions known to be elicited by IFN-γ. However, its costimulatory activities for proliferation of Th1 cells and interferon-γ production by Th1 cells are independent of the actions of IFN-γ. There is now substantial evidence that imbalances in type 1 and type 2 T cell responses may be involved in several chronic organ-restricted immune-mediated disorders, such as autoimmune thyroiditis and Crohn’s disease.

The immune response to Helicobacter pylori is considered to be a major factor contributing to gastric mucosal damage. Chronic infection with H. pylori is associated with interferon-γ-producing T cells and increased mucosal IL-12, indicative of a predominant Th1 response. IL-12 mRNA expansion levels are increased in infection with H. pylori, up-regulates the expression of IL-18 receptors on both Th1 and NK cells. Evidence for involvement of IL-18 in Crohn’s disease was provided by recent studies, in which high levels of mature IL-18 protein were identified predominantly in active Crohn’s disease and not in ulcerative colitis.

To date, whether H. pylori infection induces gastric mucosal IL-18 has not been investigated. The aims of the present study were to investigate whether H. pylori infection is associated with increased gastric mucosal IL-18 mRNA and alterations in IL-18 isoforms, to determine whether IL-18 mRNA expression differs in infection with H. pylori, and to investigate whether the presence of mature IL-18 protein is related to the presence of active caspase-1.

Patients and Methods

Patients. Gastric mucosal biopsy samples were obtained from 84 patients (44 men and 40 women; age range, 19–70 years; mean...
**Table 1.** Primer sequences for reverse-transcription–polymerase chain reaction analysis.

<table>
<thead>
<tr>
<th>Specificity direction</th>
<th>Primer</th>
<th>Product size, bp</th>
</tr>
</thead>
<tbody>
<tr>
<td>G3PDH Sense</td>
<td>GAGTCAACGGAATTGTCGT</td>
<td>158</td>
</tr>
<tr>
<td>Antisense</td>
<td>GGTGCCATGGGATTTGCCCAT</td>
<td></td>
</tr>
<tr>
<td>Interleukin-18 Sense</td>
<td>GCTTGAATACTTTAATGTAC</td>
<td>335</td>
</tr>
<tr>
<td>Antisense</td>
<td>CAAATGTCATCTATATCATGG</td>
<td></td>
</tr>
<tr>
<td>ureA Sense</td>
<td>GCCAATGGTAAATTATGTTAGT</td>
<td>411</td>
</tr>
<tr>
<td>Antisense</td>
<td>CTCCTTAAATTTTTTAC</td>
<td></td>
</tr>
<tr>
<td>cagA Sense</td>
<td>GATAACGCTGTCGCTTACATCG</td>
<td>409</td>
</tr>
<tr>
<td>Antisense</td>
<td>CTGCAAAAAGATTGTGGGCAGA</td>
<td></td>
</tr>
</tbody>
</table>

**NOTE.** G3PDH, glyceraldehyde-3-phosphate dehydrogenase.

**Cell culture.** Gastric epithelial cell lines Kato-3 (European Collection of Cell Cultures, Porton Down UK), ST-42 [24] (provided by S. Watson, Academic Unit of Cancer Studies, University of Nottingham, Nottingham, UK), MKN-1, and MKN-28 [25] (provided by Y. Luqmani, Department of Medical Oncology, Charing Cross Hospital, London) were routinely maintained in RPMI 1640 (ICN-Flow Laboratories), supplemented with 10% fetal calf serum (SeraLab) and 40 μg/mL gentamicin.

**RT-PCR for ureA, cagA, and IL-18.** RNA was extracted from gastric mucosal biopsy specimens and gastric epithelial cells by use of a cationic detergent–based extraction method (Catrimox-14; Iowa Biotechnology), as described elsewhere [26]. RNA samples were treated with 1 U of DNase I (Life Technologies) and were reverse-transcribed, as described elsewhere [26]. cDNA was amplified by PCR with primers specific for IL-18 [27], the housekeeping gene glyceraldehyde-3-phosphate dehydrogenase (G3PDH), ureA, and cagA. The sequences of oligonucleotide primer pairs are shown in table 1. PCR reactions were done in 20 μL of 10 mM Tris-HCl buffer (pH 8.3) containing 50 mM KCl, 4.5 mM (for ureA) or 1.5 mM (for IL-18, G3PDH, and cagA) MgCl₂, 200 μM dNTPs, 1 U of Taq DNA polymerase (Promega), and 20 pmol (for IL-18, ureA, and cagA) or 10 pmol (for G3PDH) of primer. Thermal cycle conditions were as follows: 95°C for 5 min for pre-denaturing, 95°C for 1 min for denaturing, 50°C (for ureA and cagA) or 55°C (for IL-18 and G3PDH) for 1 min for annealing, and 72°C for 1 min for extension. cDNA was amplified for 35 cycles (for G3PDH) or 40 cycles (for IL-18, ureA, and cagA). Negative and positive controls were included in each PCR assay. The positive control consisted of cDNA prepared from MKN-28 gastric epithelial cells. PCR was also done with use of RNA as a substrate, to confirm the absence of PCR amplicons in genomic DNA. After amplification, PCR products were separated by 2% (wt/vol) agarose gel electrophoresis and were visualized by UV light illumination. The image was analyzed by a gel documentation system (GDS 5000; Ultra Violet Products). The IL-18:G3PDH ratio was calculated as described elsewhere [28].

**Western blot analysis for IL-18 and caspase-1.** Total cellular proteins were extracted from snap-frozen gastric biopsy samples and gastric epithelial cell lines in electrophoresis sample buffer (80 mM Tris-HCl buffer, pH 6.8, containing 2.5% [wt/vol] SDS, 5% [vol/vol] 2-mercaptoethanol, 10% [vol/vol] glycerol, and 2 mM phenylmethylsulfonyl fluoride) and were heated for 10 min at

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**Figure 1.** Gel showing representative reverse-transcription–polymerase chain reaction with primers specific for interleukin-18 (IL-18; 335 bp) and glyceraldehyde-3-phosphate dehydrogenase (G3PDH; 158 bp) in gastric antral biopsy samples. Lane L, 100-bp ladder; lanes 1–3, Helicobacter pylori–negative normal mucosa; lanes 4–6, H. pylori–negative mucosa from patients with gastritis; lanes 7–9, mucosa from patients with cagA-negative H. pylori; lanes 10–12, mucosa from patients with cagA-positive H. pylori; lane 13, positive control (MKN-28 gastric epithelial cells); lane 14, negative control.
100°C. Protein lysates (40 μg) were separated on a Mini-Protein II dual cell slab system (Bio-Rad) by 13% acrylamide (T), 2.5% cross-linker (C) or 16% T, 2.5% C denaturing SDS–gel electrophoresis and were transferred onto nitrocellulose membranes (Hybond-C super; Amersham Life Science) by semidyblotting (Trans-Blot; Bio-Rad).

Multicolored standard molecular weight markers (MultiMark; Novex) were used. Recombinant 24-kDa precursor and 18-kDa mature IL-18 (gift of Russ Wilson, Imperial Cancer Research Fund, Cancer Medicine Research Unit, St. James’s University Hospital) were used as positive controls. Membranes were blocked in 10% (wt/vol) nonfat dry milk in TBS-T (0.1 Tris-HCl buffer, pH 7.6, containing 0.1% [vol/vol] Tween) for 1 h at 20°C. After washing in TBS-T and incubation (1 h at 20°C) in horse-radish peroxidase–conjugated rabbit anti–goat IgG (1:4000; DAKO) in 1% milk (wt/vol) in TBS-T, bound antibodies were detected by ECL chemiluminescence (Amersham Life Science).

Statistical analysis. The 2-tailed Fisher’s exact test and Mann-Whitney U test were used for statistical analysis. Pearson’s correlation coefficient was used to analyze the relationship between IL-18:G3PDH ratios and histologic features. P < .05 was considered statistically significant.

Results

Expression of mRNA encoding IL-18 in gastric mucosa and gastric epithelial cell lines. Antral biopsy samples were obtained from 82 patients and corpus biopsy samples from 40 patients. It was determined by endoscopy that 3 patients had gastric ulcers and 8 had duodenal ulcers; all of these patients were H. pylori positive. Twenty-six of the 40 H. pylori–positive patients were found to be cagA positive by RT-PCR. Twenty-nine of the 42 H. pylori–negative patients had normal gastric mucosa, as determined by histologic assessment, and the remaining 13 had some gastritis.

RT-PCR experiments were done, to characterize the presence of IL-18 mRNA transcripts in gastric biopsy samples and gastric epithelial cell lines. A representative RT-PCR result is shown in figure 1. IL-18 transcripts were detected in all 4 gastric epithelial cell lines (Kato-3, ST-42, MKN-1, and MKN-28; figure 2). In the antral mucosal biopsy samples, IL-18 mRNA positivity was observed significantly more frequently (P < .001) in H. pylori–positive subjects than in the H. pylori–negative patients with normal gastric mucosa (table 2). In the H. pylori–negative patients, IL-18 mRNA positivity was significantly (P < .05) more frequent in those with gastritis than in those with normal mucosa, as determined by histologic assessment. In the corpus mucosa, no significant differences were observed between the presence of IL-18 mRNA in H. pylori–positive and –negative patients (table 2).

In the antral mucosa, expression of IL-18 mRNA was significantly greater (P < .01) in H. pylori–positive patients (median IL-18:G3PDH ratio, 0.93 [interquartile range, 0.00–2.43]; n = 40) than in H. pylori–negative subjects (median, 0.18 [interquartile range, 0.00–2.21]; n = 29) with normal mucosa (fig-

Table 2. Expression of interleukin-18 (IL-18) mRNA in gastric mucosa of Helicobacter pylori–positive and –negative patients.

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Antrum</th>
<th>Corpus</th>
</tr>
</thead>
<tbody>
<tr>
<td>H. pylori negative</td>
<td>27/42 (64)</td>
<td>11/17 (65)</td>
</tr>
<tr>
<td>Normal</td>
<td>15/29 (52)</td>
<td>7/10 (70)</td>
</tr>
<tr>
<td>Gastritis</td>
<td>12/13 (92)</td>
<td>47/57 (85)</td>
</tr>
<tr>
<td>H. pylori positive</td>
<td>39/40 (98)</td>
<td>15/23 (65)</td>
</tr>
<tr>
<td>cagA negative</td>
<td>13/14 (93)</td>
<td>58/63 (91)</td>
</tr>
<tr>
<td>cagA positive</td>
<td>26/26 (100)</td>
<td>10/15 (67)</td>
</tr>
</tbody>
</table>

a P < .001 vs. H. pylori–positive patients.
b P < .005 vs. H. pylori–negative patients with gastritis.

Figure 2. Gel showing representative reverse-transcription–polymerase chain reaction for interleukin-18 (IL-18; 335 bp) and glyceraldehyde–3–phosphate dehydrogenase (G3PDH; 158 bp) in gastric epithelial cell lines. Lane L, 100-bp ladder; lane 1, Kato-3; lane 2, ST-42; lane 3, MKN-1; lane 4, MKN-28; lane 5, negative control.

Figure 3. Semiquantitative analysis of interleukin-18 (IL-18) mRNA expression in antral and corpus mucosa in Helicobacter pylori–positive and –negative patients. Levels of IL-18 relative to glyceraldehyde–3–phosphate dehydrogenase (G3PDH) are indicated on the y axis. H. pylori–positive (+) patients had significantly greater mRNA expression (P < .01, Mann-Whitney U test) than did H. pylori–negative (−) patients with normal mucosa. NS, not significant.
In antral mucosal biopsy samples of all *H. pylori*–positive (n = 9) and –negative patients (n = 9), the polyclonal antibody labeled 24- and 18-kDa proteins that comigrated with recombinant IL-18 precursor and recombinant mature IL-18, respectively (figure 5). The level of immunoreactive mature IL-18 was greater than that of precursor IL-18. In some infected and uninfected patients, an immunoreactive protein of ~30 kDa was also observed in antral biopsy samples.

In corpus mucosa, 18-kDa mature IL-18 was detected in all *H. pylori*–positive (n = 10) and *H. pylori*–negative (n = 10) patients, but, in contrast to the antrum, little 24-kDa precursor IL-18 was present. In addition, an immunoreactive 16-kDa protein corresponding to inactive IL-18 [29] was detected in both infected and uninfected corpus biopsy samples (figure 6). This 16-kDa immunoreactive protein was not observed in any of the antral biopsy samples examined.

Western blot analysis of cell lysates of gastric epithelial cells detected a 24-kDa protein corresponding to precursor IL-18 in all 4 cell lines (figure 7). However, mature 18-kDa IL-18 and a 16-kDa immunoreactive protein were detected only in Kato-3 cells (figure 7).

Expression of caspase-1 protein in gastric mucosa. The precursor IL-18 protein is cleaved to the mature 18-kDa protein by caspase-1 [4, 5]. The 45-kDa precursor caspase-1 protein similarly requires enzymatic cleavage to 20-kDa and 10-kDa subunits to be activated [30]. To investigate whether the presence of mature 18-kDa IL-18 in the gastric mucosa is associated with the active form of caspase-1, gastric biopsy samples and gastric epithelial cell lines were examined by Western blotting with a polyclonal antibody that recognizes both its 45-kDa precursor and recombinant mature IL-18, respectively (figure 4).

**Table 3.** Expression of interleukin-18 (*IL-18*) mRNA in antral mucosa of patients with and without peptic ulceration.

<table>
<thead>
<tr>
<th>Endoscopic diagnosis, <em>Helicobacter pylori</em> status (n)</th>
<th><em>IL-18</em>:<em>G3PDH</em> mRNA ratio, median (interquartile range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peptic ulcer, <em>H. pylori</em> positive (3 gastric, 7 duodenal)</td>
<td>0.95 (0.77–1.22)(^a)</td>
</tr>
<tr>
<td>Non-ulcer dyspepsia</td>
<td></td>
</tr>
<tr>
<td><em>H. pylori</em> positive (30)</td>
<td>0.93 (0.68–1.25)(^b)</td>
</tr>
<tr>
<td><em>H. pylori</em> negative (42)</td>
<td>0.27 (0.00–0.67)(^ab)</td>
</tr>
</tbody>
</table>

\(^{a}\) *P* < .005 vs. *H. pylori*–negative patients with non-ulcer dyspepsia.

\(^{b}\) *P* < .001 vs. *H. pylori*–negative patients with non-ulcer dyspepsia.
Figure 5. Representative Western blot analysis of gastric antral mucosal biopsy samples from Helicobacter pylori-infected (A) and H. pylori-negative (B) patients with normal mucosa, as determined by histologic assessment. Lanes 1–5, antral biopsy samples. Recombinant (r) 24-kDa precursor interleukin-18 (pro–IL-18) and 18-kDa mature IL-18 were used as positive controls. Pro–IL-18 and mature IL-18 were detected in both infected and uninfected subjects. Sizes of protein standards (kDa) are indicated at left.

Figure 6. Representative Western blot analysis of gastric corpus mucosal biopsy samples from Helicobacter pylori-positive (A) and ±negative (B) patients with normal mucosa, as determined by histologic assessment. Left panel, Western blot of recombinant (r) 24-kDa precursor interleukin (IL)–18 and 18-kDa mature IL-18. Lanes 1–5, corpus biopsy samples. Mature 18-kDa IL-18 protein was detected in both H. pylori–positive and ±negative patients, but little 24-kDa precursor IL-18 was present. Additional 16-kDa immunoreactive protein is evident in both A and B. Sizes of protein standards (kDa) are indicated at left.

Discussion

IL-18, a cytokine with pleiotrophic immunomodulatory functions, is increased in a variety of human inflammatory conditions, including Crohn’s disease [21, 22], rheumatoid arthritis [31], and tuberculoid leprosy [32]. In this study, we determined the levels of IL-18 transcripts in human gastric mucosa and demonstrated that H. pylori infection is associated with increased gastric IL-18 transcripts in the antral mucosa. Interestingly, however, IL-18 transcripts were present in 52% of H. pylori–negative subjects with normal antral mucosa, as determined by histologic assessment, which suggests either constitutive expression of IL-18 or up-regulation via another factor independent of H. pylori and gastritis. In this regard, it has been demonstrated that IL-18 transcripts are also abundant in human ileal and colonic mucosa [21], in pancreas, kidney, and liver cells [27], and in many other cell types [33, 34].

In contrast to many cytokines, the half-life of IL-18 mRNA may be long [34]. Indeed, the 3′ untranslated region of IL-18 lacks an AUUA destabilization sequence. The presence of high levels of IL-18 transcripts in both infected and noninfected tissues suggests that the biologic activity of this cytokine is probably controlled posttranslationally. Consistent with this, gastric IL-18 transcript levels were markedly higher than those of IL-12 (p40) observed in our earlier study [17]. In these previous studies, no constitutive gastric expression of IL-12 p40 transcripts was found, and increases were observed only in relation to infection with cag-positive H. pylori [17]. In contrast, in the current study, although IL-18 transcripts were increased in the antral mucosa of H. pylori–infected subjects, no differences in IL-18 mRNA expression levels were observed between patients infected with cag-positive and cag-negative H. pylori strains. The lack of association with cag status, together with the lack of correlation between antral IL-18 mRNA expression and chronic and acute inflammatory scores in H. pylori–infected patients, suggests that IL-18 may not be relevant to cag-related differences in gastric histopathology. The absence of a significant increase in IL-18 transcripts in the corpus mucosa of H. pylori–infected patients may reflect the reduced inflammatory response and bacterial density at this site.

IL-18 requires posttranslational enzymatic processing to be biologically activated [4, 35]. The Western blot analysis of gastric antral biopsy samples demonstrated the presence of the mature 18-kDa isoform of IL-18 in both H. pylori–negative and ±positive subjects, and this correlated with the presence of the active p20 caspase subunit. Although previous studies on colonic mucosa of patients with inflammatory bowel disease...
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Figure 7. Representative Western blot analysis of whole-cell extracts from 4 gastric epithelial cell lines. Recombinant (r) 24-kDa precursor interleukin-18 (pro–IL-18) and 18-kDa mature IL-18 were used as positive controls. Pro–IL-18 was present in all 4 cell lines. Mature IL-18 and 16-kDa inactive IL-18 were observed only in Kato-3 cells. Sizes of protein standards (kDa) are indicated at left.

Figure 8. Representative Western blot analysis of caspase-1 in gastric antral and corpus mucosal biopsy samples. In antral mucosa, both the caspase-1 precursor form (p45) and the active form (p20) were present in *H. pylori*–positive and –negative patients. In contrast, in corpus mucosa, 30-kDa protein, which may represent an intermediate form of caspase-1, was strongly detected. Active caspase-1 was also present in the corpus mucosa of both *H. pylori*–positive and –negative patients. Sizes of protein standards (kDa) are indicated at left.

have also demonstrated coexpression of mature 18-kDa IL-18 and the active p20 subunit of caspase-1 [21], only the precursor 24-kDa IL-18 was found in normal colonic mucosa [21, 22]. The presence of both mature IL-18 and p20 caspase-1 in gastric mucosa determined to be normal by histologic assessment suggests that in the gastric mucosa, in contrast to the normal colonic mucosa, production of mature IL-18 is not down-regulated. Although Western blot analysis permits detection of posttranslational processing of IL-18 to its biologically active 18-kDa or inactive 16-kDa isoforms, the methodology is qualitative rather than quantitative. More quantitative techniques for detection of IL-18, such as ELISAs, will not distinguish between precursor IL-18, mature IL-18, and degraded isoforms. In active Crohn's disease, in which high levels of mature IL-18 protein have been demonstrated by Western blotting [21, 22], assessment of total IL-18 protein in biopsy samples by ELISA showed reduced IL-18 in involved, relative to noninvolved, mucosa [36]. This suggests that, with currently available antibodies, there is preferential recognition of the inactive 24-kDa isoform of IL-18 in ELISAs. Therefore, analysis of the balance of IL-18 isoforms by Western blotting is likely to be more relevant in studying IL-18 in inflammatory conditions [36].

All clinical biopsy samples were rapidly frozen in liquid N₂. On addition of sample buffer, tissue was immediately heated to 100°C, in a manner similar to that used with the gastric epithelial cells. In the latter, mature 18-kDa IL-18 was observed only in the Kato-3 cell line, and this related to the presence of p20 caspase-1. The presence of 18-kDa mature IL-18, a product of caspase-1 cleavage, in the gastric mucosa is likely to reflect the in vivo situation. In rodents, gastric caspase activation is considered to be a tumor necrosis factor–α–mediated process [37]. The presence of tumor necrosis factor–α in G cells of normal human mucosa [38] may be a contributory factor in gastric caspase activation and may be linked to the presence of mature IL-18 in both normal and inflamed gastric mucosa. The presence of the 18-kDa isoform of IL-18 in normal *H. pylori*–negative mucosa may be important in promoting Th1 responses in the gastric mucosa.

In colonic mucosa, macrophages have been identified as a source of activated caspase-1 in Crohn's disease [39, 40], and the proenzyme is present in normal colonic epithelial cells [41]. The origin of activated caspase-1 in gastric mucosa requires further investigation. In corpus mucosa, a 16-kDa IL-18–immunoreactive protein was also observed. This protein, which lacks the N-terminus, has no biologic activity [29].

Cleavage of both the precursor 24-kDa and mature 18-kDa IL-18 to a 16-kDa product can be mediated by caspase-3. It has been suggested elsewhere [29] that caspase-3 may have a role as a down-regulator of IL-18. Caspase-3 has been identified immunohistologically in the neck region of gastric pits, and higher labeling was evident than that in colonic epithelial cells [42]. However, comparison with IL-1β posttranslational processing [43] suggests that other proteases in the gastric mucosa could also be involved in IL-18 cleavage. Pro–IL-1β is also processed by caspase-1, but caspase-1–deficient mice can induce IL-1β–dependent inflammatory responses, which suggests a
caspase–1–independent cleavage mechanism [43]. Furthermore, although splenic cells of caspase–1–deficient mice produce markedly reduced levels of extracellular IL-18, IL-18 is not absent in cell supernatants, which implies either release of the precursor form or an alternative processing pathway [44]. Further studies on the functional activity of caspase-1 and -3 in the gastrointestinal mucosa may explain differences in IL-18 processing between the gastric and colonic mucosa.

A major source of IL-18 in intestinal and colonic mucosa is the epithelium [21, 22, 45]. Indeed, the gastric epithelial cell lines examined in this study all were found to express IL-18 transcripts and the 24-kDa precursor protein. However, mature protein was observed only in Kato-3 cell extracts. The presence of IL-18 in epithelial cells, which constitute the primary interface between pathogen and host, suggests that IL-18 may play an important role in microbial defense. Several murine studies have demonstrated that IL-18 has a key function in antimicrobial defense, protecting against cryptococcal [46], mycobacterial, and Salmonella infection [47]. Furthermore, IL-18 gene–disrupted mice are susceptible to mycobacterial infection [48]. However, some pathogens may limit or interfere with host IL-18 responses [49], and immune evasion of viruses has been linked to viral synthesis of proteins with homology to mammalian IL-18–binding protein [50, 51].

In chronic H. pylori infection, mucosal production of IL-18, together with IL-12, would be important in promoting Th1 responses and interferon-γ secretion. Studies in both humans [14–16] and primates [52] have demonstrated that the gastric T cell response to H. pylori has a Th1 profile. Furthermore, the importance of T cell responses in the generation of Helicobacter-induced gastric pathology has been recently demonstrated in T cell–deficient RAG-1−/− mice [53]. The promotion of cell-mediated responses in the gastric mucosa is likely to be an important contributor to tissue injury. However, in the present study, no difference in the levels of IL-18 transcripts was evident between H. pylori–infected patients with and without ulcers. This contrasts with previous observations on the levels of IL-12 (p40) transcripts, which were elevated in patients with duodenal ulcer disease [17]. Interestingly, IL-12, but not IL-18, significantly increases T cell–mediated tissue injury in human fetal gut explants [54].

The functional role of IL-18 in Helicobacter-induced gastric inflammation and the contributions of different mucosal cell populations to gastric IL-18 production require further investigation. Helicobacter infection of IL-18–deficient mice could determine the in vivo role of IL-18 in gastric immune responses [7].

In conclusion, the present study indicates that gastric IL-18 mRNA expression is increased by H. pylori infection. The presence of the mature form of IL-18 in both normal and gastric mucosa suggests that gastric IL-18 has an important role in promoting local production of interferon-γ and cell-mediated responses in the gastric mucosa.

Acknowledgment

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References


