Persistent Infection by *Helicobacter pylori* Down-Modulates Virus-Specific CD8+ Cytotoxic T Cell Response and Prolongs Viral Infection

Mutsunori Shirai, Tatsumi Arichi, Teruko Nakazawa, and Jay A. Berzofsky

To determine whether *Helicobacter pylori* infection affects clearance of a concomitant viral infection and cytotoxic T lymphocyte (CTL) and cytokine response to that infection, *H. pylori*–infected BALB/c mice were challenged with a recombinant vaccinia virus expressing human immunodeficiency virus type 1 gp160. Two *H. pylori* strains, a colonizing clinical isolate (KS612) and an established standard noncolonizing strain (NCTC11637), were compared. Clearance of recombinant vaccinia virus was reduced in KS612-infected mice compared with NCTC11637-infected and control mice. As a potential mechanism, in contrast to control or NCTC11637-infected mice, the *H. pylori* clinical isolate KS612 diminished gp160-specific and vaccinia virus–specific CTL activity, even in the presence of exogenous interleukin-2. Furthermore, KS612-infected mice had reduced Th1 cytokine responses to gp120 in vitro compared with control or NCTC11637-infected mice. These results have implications for possible effects of prevalent *H. pylori* infection on other human diseases.

*Helicobacter pylori*, a gram-negative spiral bacterium first isolated in 1982 from a patient with chronic active gastritis [1], is responsible for a large portion of chronic gastritis and nearly all duodenal ulcers, most gastric ulcers, and probably an increased risk of gastric adenocarcinoma [2, 3]. More than 50% of the adult population is infected with *H. pylori*, in developing as well as in developed countries [4]. *H. pylori* infection is also common (40%–55%) in human immunodeficiency virus type 1 (HIV-1)–positive patients [5, 6]. Antibiotic therapy for gastroduodenal ulcers associated with *H. pylori* infection was recently introduced and found to be effective. However, a prophylactic vaccine may prevent reinfection and result in long-term eradication of the bacterium from the population by herd immunity, in addition to being more cost-effective. Elucidation of the natural immunologic response during the pathogenesis of *H. pylori* infection is important for developing strategies of immunotherapy as well as vaccines and for the treatment or prevention of ulcer formation and carcinogenesis.

Little is known of the function that T cells and cellular immunity play in *H. pylori*–associated diseases. The primary T cell response that might contribute to protection against *H. pylori* should be a CD4+ T cell response, which regulates antibody production by B cells as well as other local inflammatory reactions to mediate protection in vivo, since *H. pylori* is an extracellular bacterium [7]. *H. pylori* infection of gastric mucosa is characterized by an increased secretion of the cytokines tumor necrosis factor-α (TNF-α) and interleukin (IL)-6 and -8 [8, 9]. Also, *H. pylori* was found to stimulate peripheral blood lymphocytes to proliferate and secrete cytokines interferon (IFN)-γ and TNF-α in sensitized (i.e., antibody-positive) and nonsensitized patients [10]. An overreaction of Th2 activation might be responsible for the inadequacy of the immune system to cure *H. pylori* infection. The finding of a low secretion of IFN-γ in lymphocyte cultures with *H. pylori* in antibody-positive patients is consistent with this hypothesis [10]. It has been shown that heat-shock protein homologs of *H. pylori*, HspA and Hsp B, elicit high levels of *H. pylori*–specific IgG1 antibodies and confer immunity to gastric mucosal infections in mice previously immunized with *H. pylori* antigens. This response is likely to be mediated by a predominantly Th2-type immune response, which favors a switch to the IgG1 isotype [11]. However, in other studies in mice, a predominant Th1-like response was seen to *Helicobacter felis* infection, although IL-4 production was seen in immunized and challenged mice [12]. Thus, the cytokine balance may depend on the specific system studied.

In certain infectious diseases in mice and humans, the Th1 pattern of cytokines is associated with resistance to infection, whereas the Th2 pattern is associated with progression of infection [13–23]. It also has been reported that a switch from the Th1 to the Th2 cytokine phenotype is a critical step in the progression of HIV disease [23–25]. We previously reported down-regulation of Th1 cytokines and increased production of Th2 cytokines in response to nonparasite antigens during the patent phase of *Schistosoma mansoni* infection, with concomitant suppression of antiviral CD8+ cytotoxic T lymphocyte

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Reprints or correspondence: Dr. Jay A. Berzofsky, Molecular Immunogenetics and Vaccine Research Section, Metabolism Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland
(CTL) activity and delayed clearance of virus [14, 26, 27]. Given this interest in the interaction between disease organisms, the precedent from *S. mansoni* infection that infection with one organism might influence the immune response to another pathogen, and the prevalence of *H. pylori* in HIV-infected persons [5] and the possibility that it might be a cofactor in HIV-mediated disease, we asked whether *H. pylori* would influence the clearance of a viral infection in otherwise healthy mice. Further, CD8+ CTL responses to nonbacterial antigens during *H. pylori* infection have not been previously investigated. Because CD8+ CTL responses to viral infection often require CD4+ helper T cells and IL-2 and IFN-γ [28–35] produced by the Th1 subset thereof, and because it was also possible that one or more of the Th2 cytokines might affect CTL responses, we asked whether *H. pylori* infection might also affect CTL responses to an infection with live virus. If so, *H. pylori* infection could potentially impair immune protection against natural viral infection and contribute as a cofactor in HIV-mediated immunodeficiency.

**Materials and Methods**

**Recombinant vaccinia viruses.** vSC-8 (recombinant vaccinia virus containing the *Escherichia coli* lacZ gene) and vPE16 (recombinant vaccinia virus expressing the HIV-1gp160 envelope glycoprotein without other structural or regulatory proteins of HIV; gifts of Patricia Earl and Bernard Moss, NIAID, NIH) have been described [36, 37] and were used for immunizing the mice to induce HIV envelope–specific CTL.

**Mouse and *H. pylori*.** Eight-week-old specific pathogen–free female BALB/c mice (Japan Charles River Laboratories, Tokyo), previously shown to be free of Helicobacter organisms, were oro-gastrically administered three times at 2-day intervals an aliquot of 10^7 cfu of a fresh clinical isolate of *H. pylori* (KS612), which can colonize in the murine stomach and were reisolated from the colonized murine stomach, or an established standard control strain was quantitated by comparison to standard curves constructed with *Helicobacter* (Kirkegaard & Perry, Gaithersburg, MD). The amount of cytokine produced by the Th1 subset thereof, and because it was also possible that one or more of the Th2 cytokines might affect CD4+ cells and CD8+ cells were heat-inactivated and sonicated on ice for 50 s three times at 20-s intervals with a sonifier (Branson Ultrasonics, Danbury, CT) in the presence of glass beads. After removal of the beads, the sonicate was centrifuged at 40,000 g for 1 h at 40°C. The supernatant was filtered and stored in aliquots at −20°C. Protein contents were determined by the Lowry method.

**Measurement of cytokine responses.** Twenty days after vaccinia virus infection, spleens were removed, single cell suspensions were prepared, and erythrocytes were lysed by osmotic lysis. Spleen cells were then washed with 50% PBS and 50% Dulbecco’s modified Eagle medium (containing 100 U of penicillin/mL, 100 μg of streptomycin/mL, 80 μg of gentamicin/mL, 2 mM l-glutamine, 30 mM HEPES, 50 μM 2-mercaptoethanol, and 10% fetal bovine serum), resuspended in the same complete medium at 5 × 10^6 cells/mL (0.2-mL volume) in 96-well flat-bottomed microtiter plates (Costar, Cambridge, MA), and incubated at 37°C in 5% CO2 and 95% air with gp120 (2 mg/mL). For IL-2 measurements, an anti–IL-2 receptor monoclonal antibody (7D4) [41] was added to each well at the initiation culture (final concentration, 5 mg/mL) to block IL-2 consumption. Supernatants were collected after 24 h for IL-2 and IL-4 measurements. IL-2 and IL-4 were measured by stimulation of proliferation ([3H]thymidine incorporation; Amersham, Amersham, UK) of CTL and CT.45 cell lines [26, 42], respectively. The amount of cytokine was quantitated by comparison to standard curves of [3H]thymidine incorporation induced by known amounts of recombinant IL-2 or IL-4 (Genzyme, Cambridge, MA). The immune cells were also stimulated in vitro after treatment with both anti–CD8 monoclonal antibody (3.155; rat IgM) [43] plus complement, anti–CD4 monoclonal antibody (RL.174; rat IgM) [44] plus complement, or complement alone.

Supernatants were collected after 72 h of culture for IFN-γ measurement. IFN-γ was measured by two-site ELISA [45], using immobilized monoclonal antibody HB170 anti–IFN-γ, a polyclonal rabbit anti-mouse IFN-γ antibody, and peroxidase-conjugated donkey anti-rabbit IgG (Jackson ImmunoResearch Laboratories, West Grove, PA) followed by ABTS substrate (Kirkegaard & Perry, Gaithersburg, MD). The amount of cytokine was quantitated by comparison to standard curves constructed with recombinant IFN-γ (Genentech, South San Francisco).

The differences remained qualitatively similar when normalized for percentage of spleen cells that were CD4+ and CD8+ as determined by flow cytometry. The difference in CD4+ and CD8+ spleen cells was not significant between each group as determined by flow cytometry (data not shown).

**CTL generation.** Twenty days after vaccinia virus infection, immune spleen cells were inoculated into 24-well culture plates (5 × 10^6/mL) in complete T cell medium (1:1 mixture of RPMI 1640 and Eagle-Hanks amino acid medium containing 10% fetal calf serum, 2 mM l-glutamine, 100 U of penicillin/mL, 100 μg of streptomycin/mL, and 5 × 10^{-3} M 2-mercaptoethanol). Next, cells were restimulated for 6 days in vitro with either 2 × 10^7 gp160–transfected H-2b fibroblasts (15-12 cells)/mL, mitomycin C–treated (100 μg/mL) for 30 min at 37°C, or 2.5 × 10^5 syngeneic spleen cells infected with vSC-8 (recombinant vaccinia virus expressing the β-gal gene without any genes of HIV-1)/mL [36] for 1 h at 37°C at an MOI of 10. The IL-2 source was 10% concanavalin A supernatant–containing medium (rat T cell Monoclonal; Collaborative Research, Bedford, MA).
**CTL assay.** Cytolytic activity of in vitro secondary CTL after 6 days was measured as previously described \[46, 47\] by a 6-h assay with 5000 \(^{3}H\)Cr-labeled targets/well at the effector-to-target cell ratio indicated. Targets included 15-12 transfected, P18-pulsed (1 \(\mu\)M) BALB/c 3T3 fibroblasts or the same unpulsed as a negative control. Lysis of control 3T3 fibroblasts was <5% in all cases. The percentage of specific \(^{3}H\)Cr release was calculated as 100{[(experimental release – spontaneous release) / (maximum release – spontaneous release)]}. Maximum release was determined from supernatants of cells that were lysed by addition of 5% Triton X-100. Spontaneous release was determined from target cells incubated without adding effector cells.

**Vaccinia virus elimination study.** At 3, 7, 14, and 28 days after infection, 3 mice from each group were sacrificed, and liver and spleen tissues were aseptically removed, weighed, and frozen at \(-80°C\) before analysis of virus titer as described \[14\]. The lower limit of detection was 70 pfu/g, corresponding to a \(\log_{10}\) of 1.85.

### Results

All mice infected with a fresh clinical isolate (KS612) showed *H. pylori* colonization in their stomach, while no *H. pylori* colonization was detected in the control mice inoculated with an established standard control strain (NCTC11637) or saline alone (data not shown). To assess the effect of *H. pylori* infection on immune responses to a virus, BALB/c mice infected with *H. pylori* were inoculated intravenously with vPE16, a recombinant vaccinia virus expressing the HIV-1 gp160 envelope protein. The virus was given 2 weeks after the *H. pylori* infection. To assess whether the *H. pylori* infection might affect the clearance of recombinant vaccinia virus in vivo in vaccinia-infected H-2\(^d\) mice, we measured the clearance of vaccinia virus from different tissues at various times after infection in control or *H. pylori*-infected mice. Three H-2\(^d\) mice per group were sacrificed at days 3, 7, 14, and 28 after vaccinia virus infection, and virus titers in the liver and spleen were measured (table 1). At the time points examined, no virus was detected in the livers, and the virus was detected in the spleen of mice infected with vaccinia virus alone (i.e., control mice not infected with *H. pylori*) only at day 3. Infection with the noncolonizing control strain of *H. pylori* NCTC11637 did not affect this outcome. However, viral clearance from liver and spleen tissues from the mice infected with the colonizing strain KS612 of *H. pylori* was delayed by 3 days in the spleen and at least 14 days in the liver (table 1). Thus, colonizing *H. pylori* infection does indeed affect the ability of mice to handle a concomitant viral infection.

Given our experience with a similar suppression of viral clearance in the parasitic disease schistosomiasis \[14\], we hypothesized that the delayed viral clearance in *H. pylori* infection was due to an impairment in the induction of CD8\(^{+}\) CTL responses to the viral antigens. To test this hypothesis, we tested mice infected with gp160 expressing vaccinia virus with or without *H. pylori* infection for the ability to mount a gp160-specific CTL response. Spleen cells from the mice infected with gp160-expressing recombinant vaccinia virus (vPE16) alone, vPE16 and *H. pylori* (KS612 or NCTC11637), or *H. pylori* (KS612) alone were stimulated in vitro with the BALB/c 3T3 fibroblast transfected (15-12) expressing gp160 (or P18, an immunodominant epitope peptide of gp160; data not shown). Mice infected with vPE16 alone generated strong CTL activity against gp160 and P18 (figure 1). Specific lysis was substantial at effector-to-target ratios as low as 3:1 in those mice. However, mice infected with *H. pylori* KS612 prior to the gp160-expressing vaccinia virus infection failed to generate comparably high CTL activity against the gp160-expressing transfected, 15-12 (figure 1A), or P18 (figure 1B) at all effector-to-target ratios tested, whereas the mice infected with control strain *H. pylori* NCTC11637 prior to vaccinia virus infection mounted strong CTL responses to the gp160 or P18 superimposable on those of the mice infected with vPE16 alone. These CTL responses were specific for P18, a CTL immunodominant epitope of gp160, and failed to lyse BALB/c 3T3 fibroblast targets that express none of the HIV-1 envelope (gp120 or gp160) antigen (data not shown). Since 15-12 expresses major histocompatibility complex class I molecules but not class II, CTL must recognize the epitope in the context of class I molecules. Mice infected with *H. pylori* alone failed to mount CTL activity against gp160. Thus, colonization of *H. pylori* KS612 resulted in reduced CTL generation against gp160 (3- to 9-fold in lytic units), whereas the noncolonizing strain, NCTC11637, failed to diminish the CTL response. This modest reduction in lytic

### Table 1. Delayed clearance of vaccinia virus in tissues of mice coinfected with *H. pylori.*

<table>
<thead>
<tr>
<th>Day</th>
<th>Vaccinia plus KS612</th>
<th>Vaccinia plus NCTC11637</th>
<th>Vaccinia alone</th>
<th>Liver</th>
<th>Vaccinia plus KS612</th>
<th>Vaccinia plus NCTC11637</th>
<th>Vaccinia alone</th>
<th>Spleen</th>
</tr>
</thead>
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<tr>
<td>3</td>
<td>7.20 ± 0.24</td>
<td>–</td>
<td>–</td>
<td>4.65 ± 0.12</td>
<td>2.65 ± 0.40</td>
<td>3.82 ± 0.20</td>
<td></td>
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</tr>
<tr>
<td>7</td>
<td>5.39 ± 0.25</td>
<td>–</td>
<td>–</td>
<td>2.33 ± 0.22</td>
<td>–</td>
<td>–</td>
<td></td>
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</tr>
<tr>
<td>14</td>
<td>2.97 ± 0.31</td>
<td>–</td>
<td>–</td>
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**NOTE.** Results are \(\log_{10}\) titer (pfu/g) (means ± SDs of 3 mice/group). –, below limit of detection.
Figure 1. Anti-gp160 CTL responses from mice primed in vivo with recombinant vaccinia virus. *H. pylori*–infected or uninfected mice were infected with recombinant vaccinia virus vPE16 expressing gp160 of human immunodeficiency virus (HIV)-1 2 weeks after *H. pylori* infection and sacrificed 20 days later. Spleen cells were restimulated in vitro with gp160 gene–transfected H-2d fibroblasts (15-12 cells) (A, B) [46] or syngeneic spleen cells infected with vSC8 (recombinant vaccinia virus expressing β-gal gene without any genes of HIV-1) (C) [36], in presence of 10% rat T cell Monoclonal (Collaborative Research, Bedford, MA) as source of interleukin-2; 6 days later, specificity of CTL effectors was tested against 51Cr-labeled 15-12 transfectant (A), P18-pulsed (1 μM) BALB/c 3T3 fibroblast cells (H-2d class I major histocompatibility complex–positive, class II negative) (B), vSC-8—infected (MOI = 10) 3T3 fibroblasts (C), or untransfected, unpulsed 3T3 fibroblasts as negative control (data not shown) at effector-to-target ratio indicated. Lysis of control 3T3 fibroblasts was <5% in all cases. Data represent mean responses of 5 mice per time point ± SE. Similar results were obtained in 2 additional experiments. * P < .01, ** P < .05 by Student’s t test.
units is sufficient to almost completely eliminate killing at low effector-to-target ratios that may reflect the situation in vivo (e.g., at 3.7:1 in figure 1A).

To examine the effect on vaccinia virus–specific CTL, the splenic cells from mice infected with vaccinia virus alone, vaccinia virus and H. pylori (KS612 or NCTC11637), or KS612 alone, after restimulation with control vaccinia virus vSC8-infected 3T3 fibroblasts and IL-2 (at exogenous IL-2 levels during CTL generation in vitro sufficient to compensate for deficiency in T cell help in vitro), were tested for CTL activity against epitopes of the vaccinia virus itself. The vaccinia virus–specific CTL activity was also reduced (3- to 9-fold in lytic units) in the mice doubly infected with vaccinia virus plus KS612 compared with mice infected with vaccinia virus alone or vaccinia virus plus NCTC11637 (figure 1C). No CTL activity against vaccinia virus was detected in mice infected with KS612 or NCTC11637 alone (data not shown). These specific CTL were found to be CD8+CD4− (data not shown). The differences seen in figure 1 remained qualitatively similar when normalized for percentage of spleen cells that were CD8+ as determined by flow cytometry. There was no significant difference in CD8+ spleen cell numbers between groups as determined by flow cytometry (data not shown).

The mechanism of inhibition of CTL induction by colonizing H. pylori infection is not clear but might be related to a shift in cytokine production from Th1-like to Th2-like, given the similar experience in schistosomiasis [14] and the known effect of H. pylori on in vitro cytokine production by lymphocytes from infected patients [10]. Therefore, we tested whether cytokine production to HIV-1 envelope protein was affected by H. pylori infection in gp160–vaccinia virus doubly infected mice. Twenty days after viral infection, we found that the Th1 cytokine (IFN-γ and IL-2) responses to the gp120 antigen expressed by the recombinant vaccinia virus were down-regulated in all mice inoculated with the colonizing strain KS612 and vaccinia virus (figure 2A and 2B). Splenic cells from the mice infected with vaccinia virus alone or mice inoculated with vaccinia virus and the noncolonizing strain NCTC11637 produced high levels of IFN-γ and IL-2 in response to in vitro stimulation with recombinant gp120 but lower IL-4 levels to H. pylori antigens (figure 2). Figure 2 also shows no detectable H. pylori–specific cytokine production in the mice infected with vaccinia virus alone and those infected with vaccinia virus and noncolonizing NCTC11637. Conversely, spleen cells from KS612-infected mice and KS612–vaccinia virus doubly infected mice showed reduced IFN-γ and IL-2 production against the stimulation with H. pylori or gp120 (figure 2A and 2B) and modest IL-4 production in response to H. pylori but little to gp120 (figure 2C). Although IL-4 production even by KS612-infected mice was modest, that to H. pylori was statistically significantly greater than the IL-4 production by mice infected with the control NCTC11637 strain. IFN-γ, IL-2, and IL-4 were all found to be produced primarily by CD4+ T cells, in experiments in which CD4+ or CD8+ T

Figure 2. Cytokine production in vitro in response to recombinant gp120 or H. pylori antigens in mice infected with vaccinia virus, vaccinia virus and H. pylori, or H. pylori alone. Mice were infected with H. pylori; 2 weeks later, these and uninfected control mice were infected with recombinant vaccinia virus vPE16 expressing gp160; 20 days later, spleens were removed, and single-cell suspensions were prepared, resuspended in culture medium, and incubated with gp120 (2 μg/mL) or H. pylori antigens (HP; 20 μg/mL). Supernatants were collected and assayed for interferon (IFN)-γ (A), interleukin (IL)-2 (B), and IL-4 (C), expressed as amount/10⁶ cells present. Data represent mean responses of 5 mice per time point ± SE. Similar results were obtained in 2 additional experiments. * P < .01, ** P < .05 by Student’s t test.
cells were selectively deleted by treatment with monoclonal antibodies and complement (figure 3). The differences seen in figure 2 remained qualitatively similar when normalized for percentage of spleen cells that were CD4+ as determined by flow cytometry. There was no significant difference in CD4+ spleen cells between each group as determined by flow cytometry (data not shown).

**Discussion**

CD4+ T cell responses to viral antigens are important in controlling infection by providing help for B cell humoral and CD8+ T cell responses protective against the disease, as well as producing protective cytokines themselves. It was suggested that a strong T cell response to HIV proteins is associated with a favorable course of the infection [22, 48–68]. CTL may contribute to elimination of virus. We have found that impaired anti-gp160 or anti-vaccinia virus CTL responses are associated with delayed or diminished clearance of virus or virus-infected cells [14, 69].

Over the last decade, Th1-type CD4+ cells producing IL-2 and IFN-γ and Th2-type CD4+ cells producing IL-4 and IL-5 have been identified in mice and humans [13, 70–72]. In certain chronic infectious parasitic, bacterial, and viral diseases, the Th1 pattern of cytokines is associated with resistance to infection, whereas the Th2 pattern is associated with progressive forms of infection, with a few exceptions in some parasitic infections [13–23]. A switch from the Th1 to the Th2 cytokine phenotype has been found to occur during the course of HIV infection [63]. In the case of *Helicobacter* species, different results have been reported for the predominant cytokine response to *Helicobacter* antigens in mice, depending on the system used [11, 12]. However, cytokine production specific for non-*H. pylori* antigens has not been examined in these mice. Nevertheless, it was this analogy between *H. pylori* infection and other chronic parasitic and bacterial infections that led us to ask whether *H. pylori* infection, like *S. mansoni* infection [14, 26], would influence the immune response to other unrelated antigens and, in particular, concomitant viral infections. The results indicate that experimental *H. pylori* infection indeed induces a decrease in the ability of mice to clear even an attenuated thymidine kinase-negative recombinant vaccinia virus.

We hypothesized that this reduced viral clearance is the result of down-regulation in virus-specific Th1 cytokine and CD8+ CTL responses in the doubly infected animals. To test this hypothesis, we measured CD8+ CTL activity specific for both HIV-1 gp160 and vaccinia virus itself in mice infected with recombinant vaccinia virus expressing gp160. We found a surprising systemic defect in class I–restricted CTL responsiveness to viral antigens. The CD8+ CTL activity of spleen cells from *H. pylori*–infected mice was greatly reduced despite the presence of exogenous IL-2 during stimulation in vitro as a replacement for T cell help, indicating that if a deficiency in

![Figure 3.](https://i.imgur.com/3X5.png)
cytokine production is responsible, it must be working at the level of precursor generation and expansion in vivo. An alternative explanation is that the observed deficiency in CTL response reflects H. pylori–induced alterations in antigen-presenting cell function and/or the direct influence of down-regulatory cytokines such as transforming growth factor-β on CTL precursor generation in vivo, although this has not yet been demonstrated to be produced during H. pylori infection.

The present study also revealed that H. pylori–infected animals have diminished Th1 cytokine responses to unrelated viral antigens, not previously observed. Expression of IFN-γ and IL-2 was found, but IL-4 was barely detectable in response to gp120 in mice infected with HIV gp120–expressing vaccinia virus alone. This indicates that Th1 cytokine phenotype against gp120 protein is predominant in the course of vaccinia virus infection. The amount of IFN-γ and IL-2 expression shown in those mice was not affected by noncolonizable H. pylori inoculation. However, significantly decreased Th1 cytokine activity was measured in response to gp120 during the persistent infection of colonizable H. pylori coinfected with vaccinia virus. The reduction in IFN-γ and IL-2 expression by CD4+ T cells here may be relevant to antigen priming by gp120 in vivo and resultant CTL generation against gp120 and vaccinia virus itself, although we cannot confirm cause and effect.

The very high prevalence of H. pylori infection in both developed and developing countries suggests that these results may have important implications for the differences in ability of different persons to handle other human infectious diseases. A number of organisms have been considered as possible cofactors influencing the rate of progression of HIV-mediated disease, and our results suggest that H. pylori should be investigated as a candidate for this list. One study of intravenous drug users paradoxically found a somewhat reduced frequency of H. pylori infection in HIV-1–positive subjects (40%) compared with HIV-1 negative controls (66%), largely accounted for by a reduced frequency in those with AIDS (33%) rather than HIV-1–positive persons without AIDS (53%) [5]. However, a subsequent study that used histology found a prevalence of H. pylori infection of 55% in HIV-positive persons, with no significant difference between those with AIDS (63%) and those without (52%), but this study did note an inverse correlation with the frequency of antibiotic treatment over the 6 months before endoscopy, suggesting that antibiotic treatment of opportunistic infections might reduce the prevalence of H. pylori infection (possibly accounting for the earlier results) [6]. Thus, overall, although there is no epidemiologic evidence to indicate that H. pylori increases the rate of progression of HIV-1 to AIDS, H. pylori infection is present in about half of those with HIV-1 infection and should be examined more closely for an influence not only on progression of HIV-1 infection itself but for its possible influence on the nature or course of associated opportunistic infections.

Also, other infectious diseases known to be influenced by Th1/Th2 cytokine balance, such as mycobacterial infections, would be relevant to study for possible effects of concomitant H. pylori infection. In addition to infectious diseases, the outcome of vaccination may be influenced by H. pylori infection, especially when induction of cellular immunity is desired, such that persons infected with colonizing strains of H. pylori may not have as high levels of cellular immunity induced by the vaccine. Since H. pylori is strongly associated with an increased risk of gastric cancer [2, 3], and cellular immunity may be important in the immune surveillance against cancer, these results suggest that H. pylori may have a two-pronged effect on gastric cancer by inducing the malignancy and simultaneously inhibiting the immune defense against it. Clearly, the implications for interactions between H. pylori infection and other human infectious and neoplastic diseases warrant further examination.

Acknowledgments

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References

11. Ferrero RL, Thibierge JM, Kansau I, Wuscher N, Huerre M, Labigne A. [6]. Thus, overall, although there is no epidemiologic evidence to indicate that H. pylori increases the rate of progression of HIV-1 to AIDS, H. pylori infection is present in about half of those with HIV-1 infection and should be examined more closely for an influence not only on progression of HIV-1 infection itself but for its possible influence on the nature or course of associated opportunistic infections.

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64. Salk J, Bretscher PA, Salk PL, Clerici M, Shearer GM. A strategy for prophylactic vaccination against HIV. Science 1993; 260:1270–2.


