The Endotoxin of *Helicobacter pylori* Is a Modulator of Host-Dependent Gastritis

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Received 23 January 1997/Returned for modification 24 March 1997/Accepted 28 May 1997

Atrophic gastritis caused by *Helicobacter pylori* is the precursor lesion in the development of intestinal-type gastric adenocarcinoma. In animal models, atrophic gastritis induced by *Helicobacter felis* has been shown to be host dependent, developing in some mouse strains and not in others. The lipopolysaccharide (LPS) of *H. pylori* has been suggested to play a role in the induction of gastritis. The goal of this study was to compare the inflammation induced by long-term infection of the C3H/He and the C3H/HeJ strains of mice with *H. felis*. C3H/HeJ mice are unresponsive to LPS. Six months after infection, severe atrophic gastritis had developed in the body mucosa of all infected C3H/He mice, with replacement of parietal and chief cells. Atrophy was associated with a loss of the *H. felis* from the antral mucosa. In contrast, no atrophy was seen in the infected C3H/HeJ non-LPS responder animals, and heavy colonization of the antrum remained. There were no significant differences between both the quantitative and qualitative serum immunoglobulin G (IgG) and salivary IgA levels in both strains of mice. The main difference between the two strains of long-term-infected mice was the inability of mice to respond to *H. felis* with the feline helicobacter *Helicobacter felis* resulted in two very different patterns of gastritis (17). BALB/c mice showed virtually no pathology, while C3H/He and C57BL/6 mice had significant inflammatory scores. They also infected a series of congenic mice and concluded probable contributions by both major histocompatibility complex (MHC) and non-MHC genes to *Helicobacter*-induced inflammation. We had previously done a similar experiment, but with long-term follow-up, and observed that the patterns of inflammation in the responsive mouse strains (SJL, C3H/He, DBA/2, and C57BL/6 mice) were very different from that seen in *H. pylori-*infected humans with antrum-predominant gastritis (20). While the bacteria were almost exclusively located in the antral glands, the inflammatory changes were restricted to the body of the stomach. As the severity of atrophy increased with time, the *H. felis* cells were lost from the antrum. This pattern of gastritis has similarities to that observed in the gastric cancer-prone populations. In the low-responsive mice (BALB/c and CBA), there was only mild inflammation with no atrophy, and the bacterial numbers remained high in the antrum for the 6 months of the study. We termed this phenomenon host-dependent gastritis and concluded that these findings challenged current concepts of the development of *Helicobacter*-induced atrophy in that active-chronic gastritis of the antrum and/or the body mucosa is not a prerequisite. We also suggested that a cell-driven autoimmune process may be responsible for this phenomenon, since the main pathology is found away from the area of colonization, suggesting that a direct effect due to toxic actions of the *Helicobacter* is not likely. This autoimmunity was proposed to be cell driven, since no autoantibodies were detected.

The mammalian host has learnt to recognize the presence of unwanted gram-negative bacteria within its tissues by respond-
ing to lipopolysaccharide (LPS) or endotoxins that comprise the outer surface molecules of these bacteria. These molecules have potent immunostimulatory activities that prime the defense systems of the host, calling in inflammatory cells to remove the invader and facilitate the induction of protective immunity. With some major pathogens which are not repelled by this initial protective response, the excess of LPS that enters the tissues following establishment of the bacterium results in an overstimulation of the immune system, with excess production of cytokines, leading to symptoms (i.e., endotoxic shock) or tissue damage.

The demonstration by both Mohammadi and ourselves that the C3H/He mouse strain showed host-dependent gastritis following *H. felis* infection provided us with an important opportunity to look at the mechanisms of induction of inflammation. The C3H/He strain is a unique mutant strain derived in 1947 from the C3H/He strain (24, 25). These animals possess a profound defect in their ability to respond to the lipid A component of endotoxin or LPS derived from the cell walls of gram-negative bacteria. Although the exact mechanism for this nonresponsiveness in these mice lacking the *lps*- gene locus is unknown, it is thought that it is related to the ability of macrophages to produce cytokines such as tumor necrosis factor alpha (TNF-α) (3). It was of obvious interest to determine the responsiveness of C3H/HeJ mice to *H. felis* infection in comparison with the wild-type strain.

**MATERIALS AND METHODS**

**Animals.** Six-week-old specific-pathogen-free female mice of the C3H/He and C3H/HeJ strains were purchased from the Walter and Eliza Hall Institute (Melbourne, Australia) and were maintained in the School of Microbiology and Immunology animal house, University of New South Wales, Sydney, Australia. All protocols involving animal experimentation were approved by the Animal Care and Ethics Committee at the University of New South Wales.

**Bacteria.** *H. felis* CS1 (ATCC 49179) was grown on campylobacter selective agar consisting of 5% (vol/vol) sterile horse blood in blood agar base no. 2 (Oxford Ltd., Basingstoke, United Kingdom) containing 10-μg/ml vancomycin (Sigma Chemical Co., St. Louis, Mo.), 5-μg/ml trimethoprim lactate (Sigma), 2,500-IU/liter polymyxin B (Sigma), and 5-μg/ml amphotericin B (E. R. Squibb & Sons, Princeton, N.J.). The plates were incubated in an anaerobic jar with a microaerophilic gas-generating kit (code no. BR 56; Oxoid) for 2 days at 37°C. *H. felis* was harvested from plates and suspended in brain heart infusion broth (Oxoid), and the final concentration was adjusted to approximately 10^8 bacteria/ml with brain heart infusion broth. For infection, mice were inoculated intragastrically in a 5-day period with 0.1 ml of bacteria sonicates, or by using a polyethylene sphincter catheter (0.38-mm internal diameter by 0.97-mm outer diameter). Uninfected control animals were kept for the same period.

*H. felis* sonicate was obtained for immunization by harvesting cells in phosphate-buffered saline and sonicating them with a Branson Sonifier fitted with a microtip (Branson Ultrasonics Corporation, Danbury, Conn.). The protein content of the sonicate was determined by the DC protein assay (Bio-Rad, Regents Park, Australia) and then stored at −20°C until use. When live *H. felis* was required for challenging, the organisms were obtained as described above.

**Experimental schedules.** (i) Assessment of colonization and pathological responses. Groups of C3H/He and C3H/HeJ mice were infected as described above and left for 4 to 6 weeks at 20°C until use. When live *H. felis* was required for challenging, the organisms were obtained as described above.

(ii) Immunization studies. Groups of C3H/He and C3H/HeJ mice (*n*= 20) were dosed orally on days 0, 7, 14, and 21 with 10^8 of *H. felis* whole-cell sonicate plus 10 μg of cholera toxin (CT) (Sigma). Age-matched animals (*n*= 10) were retained as controls. Three weeks after the last immunizing dose, both the immunized and control animals were given two challenge doses of −10^8 live *H. felis* cells 2 days apart. Three weeks after challenge, saliva and sera were collected from all animals for the assessment of levels of IgA and IgG, respectively.

Gastric samples were also taken for urease assays and determination of colonization by histology.

**Sample collection.** Mice were anaesthetized by intraperitoneal injection with 50 mg of both ketamine and xylazine (Parnell Laboratories, New South Wales, Australia), 1 mg of both ketamine and xylazine, and for the immunized mice, they were injected intraperitoneally with 0.1 mg of pilocarpine hydrochloride (Allergan, New South Wales, Australia) to stimulate salivation. Saliva samples were collected aseptically and frozen at −20°C. Blood samples were collected from the aortic arch, and the serum samples were stored at −20°C. Mice were sacrificed by cervical dislocation, and their stomachs were collected.

**Assessment of pathology and colonization.** Half of the antral region of the stomach was taken for the direct urease test (10), the remaining half of the stomach was fixed in 10% formal buffered saline and embedded in paraffin, and 4-μm-thick sections were cut. These sections were stained with hematoxylin-eosin staining for histopathological assessment and Muy Grunow-Giemsa staining for assessment of colonization. The degrees of gastric inflammation and architectural changes of gastric mucosa were assessed in the hematoxylin-eosin sections. Slides were inspected blind; the labels of all slides were masked, and slides were randomly mixed and relabelled. All slides were scored independently by two individuals (T. Sakagami and M. F. Dixon); interobserver differences were found to be negligible. The degree of gastritis was determined with the scoring system described previously (20). Antrum and body were each graded for chronic inflammation, which was characterized by infiltration of mononuclear cells, activity, and granuloma. The presence of polyomorphonuclear leukocytes, and crypt abscess was graded by the loss of specialized cells, i.e., chief and parietal cells (0, nil; 1, mild; 2, moderate; 3, severe). The degree of colonization in *H. felis*-infected mice was assessed by semiquantitative analysis of bacteria in the antrum, body, and squamous mucosa junction (0: no bacteria; 1, < 1 bacteria; 2, 1 to 2 bacteria; 3, 3 to 10 bacteria; 4, > 20 bacteria/40×). Colonization in all slides examined was also assessed blind by two individuals (T. Sakagami and J. O’Rourke). Stomach sections from the mice used in the immunization study were also assessed blind by one individual (F. Radcliffe). Animals were considered uninfected when no bacteria were visible and were considered infected when even one bacterium was visible.

**Measurement of serum IgG and salivary IgA antibodies.** Systemic IgG and salivary IgA antibodies against *H. felis* were measured by an enzyme-linked immunosorbent assay (ELISA). Microtiter (ELISA) plates were coated overnight with whole-cell sonicates of *H. felis* (10 μg/well) as the antigen. For IgG, sample sera were diluted to 1/100 and 1/200; for IgA detection, saliva was diluted 1/4 with blocking buffer (0.1 M phosphate buffer [pH 7.2], 0.02% [wt/vol] sodium azide, 1-mlg/ml gelatin). Standard positive sera (mice immunized with *H. felis* plus CT on days 0, 7, 14, and 21) were diluted to 1/100 and 1/200; for IgA detection, saliva diluted 1/4 with blocking buffer (0.1 M phosphate buffer [pH 7.2], 0.02% [wt/vol] sodium azide, 1-mlg/ml gelatin). The plates were incubated in an anaerobic jar with a microaerophilic gas-generating kit (code no. BR 56; Oxoid) for 2 days at 37°C. *H. felis* was harvested from plates and suspended in brain heart infusion broth (Oxoid), and the final concentration was adjusted to approximately 10^8 bacteria/ml with brain heart infusion broth. For infection, mice were inoculated intragastrically in a 5-day period with 0.1 ml of bacteria sonicates, or by using a polyethylene sphincter catheter (0.38-mm internal diameter by 0.97-mm outer diameter). Uninfected control animals were kept for the same period.

**Immunohistochemistry.** Frozen sections of stomach were cut at 4 μm and air dried overnight. Slides were fixed in acetone for 10 min, air dried, and stored at −20°C until use. For staining, nonspecific binding was blocked with 20% (vol/vol) normal rabbit serum and 2% (wt/vol) bovine serum albumin in (0.5 M Tris-buffered saline [pH 7.6]). For detection of macrophores and CD4 and CD8 T cells, 50 μl of a primary rat-anti-mouse antibody was applied for 1 h at 37°C. Bound antibody was detected with biotinylated rabbit-anti-rat IgG diluted 1/200 in Tris-buffered saline containing 2% (wt/vol) bovine serum albumin. For B cells, a biotinylated rat-anti-mouse B-cell antibody was used. All antibodies were obtained from Serotec, Oxford, England, Sections were incubated for 30 min at room temperature before washing and revelation of biotin with the avidin-biotin Complex Elite Vectastatin kit (Vector Laboratories, Burlingame, Calif.) and counterstaining with hematoxylin. Cellular infiltration into the lamina propria of stained sections was graded according to the following semi-quantitative values: 0, no increase in cellular infiltration; 1, uniform low level infiltration; 2, moderately severe infiltration; and 3, severe infiltration.

**Statistics.** The significance of the difference in *H. felis* infection levels between mice immunized with *H. felis* plus CT and the control mice was assessed by the chi-square test. A Mann-Whitney rank sum test was used to assess whether differences in anti-*H. felis* IgA for IgA antibody levels in the immunized and control groups were significant.
RESULTS

Endotoxin responsiveness is involved in induction of host-dependent gastritis following *H. felis* infection. To determine whether sensitivity to bacterial endotoxins was important in *Helicobacter*-induced gastritis, mice of the C3H/He and C3H/HeJ strains were orally infected with *H. felis*, and comparisons of the colonization and pathology of stomachs removed at various times after infection were made. There was a clear difference in the long-term colonizations of the two strains of mice. The C3H/He mice displayed a loss of *H. felis* infection which began within 2 months postinfection, and by six months virtually all of the mice were *Helicobacter* free (Table 1). Also, at 2 months postinfection, C3H/He mice had a high bacterial load in the antrum of the stomach, but there were few bacteria in the stomach body. There was an associated gastritis which was mainly localized in the body mucosae (see Fig. 2) and was completely absent in noninfected control animals (Fig. 1B). By 6 months, the inflammation had developed to a severe atrophic gastritis in the body of C3H/He mice and the bacterial colonization had virtually disappeared, even in the antrum, despite the lack of atrophy in this part of the stomach (Fig. 2).

In contrast, the LPS-unresponsive C3H/HeJ strain remained infected throughout the 6-month period and had only moderate gastritis in the stomach body, despite heavy bacterial colonization. Histological examination clearly demonstrated a greatly reduced inflammatory response in the C3H/HeJ mice (Fig. 3) in comparison with the endotoxin-responsive C3H/He mice (Fig. 2). The control animals again showed no evidence of gastritis (Fig. 1A).

**Cellular infiltrate.** In noninfected mice of both C3H/He and C3H/HeJ strains, very few immune cells were observed. However, the sites of inflammation of infected C3H/He mice had a very heavy infiltration of B lymphocytes and T lymphocytes, with a much higher proportion of CD4+ cells than of CD8+ cells. There was also a moderately dense infiltration of macrophages. In infected C3H/HeJ mice, there was also a heavy infiltration of B cells but only a moderate infiltration of T cells, with a more-even ratio of CD4+ to CD8+ cells. However, perhaps the most significant observation concerned the macrophages, since the stomachs from infected C3H/HeJ mice had virtually no increase in macrophage numbers compared to those of noninfected controls, whereas infected C3H/He mouse stomachs had dense macrophage infiltration of their laminae propriae (Table 2). No difference was observed between the cellular infiltrations of noninfected C3H/He and C3H/HeJ mice.

**Humoral response.** To further characterize the immune response to infection, serum samples from these mice were examined by ELISA for antibodies reactive with *H. felis* antigens. Both strains of mice generated a strong serum IgG response to *H. felis* following infection (Table 3). This response was still present in C3H/He mice at 6 months postinfection, despite the majority of animals having cleared the infection. There was also no obvious difference in the qualitative reactivities of these sera against *H. felis* proteins separated by sodium dodecyl sulfate (SDS)-polyacrylamide gel electrophoresis and transferred to nitrocellulose by Western blotting (not shown).

**Endotoxin responsiveness is not involved in induction of protective immunity by immunization with *H. felis* sonicate.** To determine whether the mitogenic activity of *Helicobacter* LPS contributed to the generation of protective immunity, the two strains of mice were immunized with *H. felis* sonicate with CT as an adjuvant before oral challenge with live *H. felis*. Following immunization, both strains of mice were protected against

<table>
<thead>
<tr>
<th>Mouse strain and time postinfection</th>
<th>% Colonization</th>
<th>Grade for antrum</th>
<th>Grade for body</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Bacteria</td>
<td>CI</td>
</tr>
<tr>
<td>C3H/He</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 mo</td>
<td>80</td>
<td>1.4</td>
<td>0.6</td>
</tr>
<tr>
<td>6 mo</td>
<td>10</td>
<td>0.1</td>
<td>0.7</td>
</tr>
<tr>
<td>C3H/HeJ</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 mo</td>
<td>100</td>
<td>2.2</td>
<td>0.3</td>
</tr>
<tr>
<td>6 mo</td>
<td>100</td>
<td>3.2</td>
<td>0.3</td>
</tr>
</tbody>
</table>

* 0, no bacteria; 1, 1 to 2 bacteria/crypt; 2, 3 to 10 bacteria/crypt; 3, 11 to 20 bacteria/crypt; 4, >20 bacteria/crypt.

**CI, chronic inflammation.** 0, no inflammation; 1, 2, and 3, mild, moderate, and severe inflammation, respectively.

**FIG. 1.** Gastric tissue from 6-month control noninfected animals. (A) C3H/HeJ mouse (magnification, ×78). (B) C3H/He mouse (magnification, ×62.4). Both figures show the normal appearance of the body mucosae, with parietal and chief cells visible.
challenge, with 95 and 85% protection in C3H/HeJ and C3H/He mice, respectively (Table 4). The small difference in protection was not statistically significant. Both sets of immunized mice had a significantly lower level of \textit{H. felis} colonization than that of the control animals. Analysis of the anti-\textit{H. felis} serum IgG (Fig. 4) and salivary IgA (Fig. 5) antibody response failed to reveal any significant difference in the humoral response between the immunized C3H/He and C3H/HeJ mice. Both sets of immunized mice had significantly higher anti-\textit{H. felis} IgG and IgA antibody responses compared to those for the \textit{H. felis}-challenged control animals (Mann-Whitney $P < 0.001$).

**DISCUSSION**

\textit{H. pylori} is a gram-negative pathogen which induces a destructive inflammation in the tissues involving an antrum-dominant gastritis or a pangastritis. However, LPS from \textit{H. pylori} has not been considered to play a major role in pathogenesis. By all of the in vitro tests available, the immunostimulatory activity of \textit{H. pylori} endotoxin is greatly reduced compared to those of pathogens such as \textit{Escherichia coli} and \textit{Salmonella} spp. (4, 19). The biological activity of the \textit{H. pylori} LPS molecule is more similar to that of \textit{Bacteroides fragilis}, which colonizes the lower bowel in humans (13, 26). The hypothesis that this was a consequence of evolution to long-term survival on the gastric surface has been proposed. Clearly, too effective an immune response against the organism would not be to its benefit. More recently, another contribution of LPS to pathogenesis has been suggested with the discovery of epitopes within the molecule with similarity to those found in the host tissue (21). There are also homologs within the polysaccharide chains of \textit{H. pylori} LPS to the ATPase that is the proton pump of the mammalian parietal cell (2). This raised the possibility of antibody-driven immunity being a part of the disease process.

The studies presented here demonstrate that the \textit{H. pylori} endotoxin molecule plays a role in the induction of one form of gastritis in mice, which we have recently proposed may be equivalent to the inflammation seen in certain populations of cancer-prone individuals (20). The C3H/HeJ mouse differs only from the wild-type C3H/He mouse by a change in a single gene located on chromosome 4 that is responsible for the ability to respond biologically to LPS, the so-called \textit{lpsd} mutation (22). While long-term infection with \textit{H. felis} in wild-type mice resulted in destructive atrophic changes in the body of the stomach, with almost complete disappearance of parietal and chief cells, no atrophy was seen in the mutant mice. In agreement with this ablation of normal gastric function in the C3H/He mice, the bacteria colonizing the antrum were almost completely eliminated. One explanation for this loss of bacteria could be that it was due to ecological changes resulting from a drop in local acid secretion (11). In the C3H/HeJ
Inflammatory response is at least partly attributable to the LPS-
the be explained by the reduced responsiveness of macrophages to
endotoxin to transcribe more messenger and do not translate
a mRNA for TNF-
alpha, they are not activated by
endotoxin to transcribe more messenger and do not translate
existing messenger into protein (3). The reduced inflammation
seen during H. pylori infection in C3H/HeJ mice can, therefore,
be explained by the reduced responsiveness of macrophages to
the Helicobacter LPS. This then indicates that the normal in-
flammatory response is at least partly attributable to the LPS-
stimulated production of inflammatory cytokines by activated
macrophages.

The fact that the humoral responses to H. felis antigen were
the same in both mutant and wild-type mice is further support
that the destructive mechanism of host-mediated gastritis is
not antibody mediated. Previously, we had shown that sera
from long-term H. felis-infected animals with host-dependent
gastritis, including C3H/He mice, did not contain antibodies
reactive against the proton pump by ELISA or against any
other gastric antigens by immunofluorescence on frozen gastric
sections (20). To some extent, this argues against the hypoth-
thesis of Appelmelk et al. that the cross-reactivity between Hel-
icobacter LPS and gastric tissue plays a role in pathogenesis
(1). However, the LPS of H. felis has not yet been comprehen-
sively analyzed, although preliminary data suggest that its
structure is different from that of H. pylori (17a).

It is important to note that there was inflammation in the
body that presumably was independent of LPS, demonstrating
the presence of another mechanism of activation. It has al-
ready been shown that H. pylori can activate macrophages by
an LPS-independent mechanism, which could explain the low
level of inflammation that we have observed in C3H/HeJ mice
(14). This emphasizes the complexity of the multifactorial pro-
cess that results in gastritis, particularly in the body of the
stomach.

Based on the findings described above and the elegant stud-
ies of Mohammadi et al., a picture of the process of induction
of host-dependent atrophic gastritis in susceptible mice
emerges. The gastric antrum becomes infected with large num-
bers of bacteria; however, unlike the situation in H. pylori-
infected humans, the presence of the bacterium is not accom-
panied by an active gastritis. This could be due to the lack of
virulence factors, such as the cagA gene, which induce inflam-
matory cytokines (such as IL-8 in humans) or due to the lack
of direct contact with the gastric surface. The studies of Mo-
hammadi et al. have demonstrated that a Helicobacter-specific
Th1 response is elicited in Helicobacter-infected mice and that
the subsequent delayed-type hypersensitivity response contrib-
TABLE 3. Levels of specific antibody against H. felis

<table>
<thead>
<tr>
<th>Mouse strain</th>
<th>2 mo postinfection</th>
<th>6 mo postinfection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control group</td>
<td>Infected group</td>
</tr>
<tr>
<td>C3H/He</td>
<td>0.09 ± 0.05</td>
<td>1.47 ± 0.24</td>
</tr>
<tr>
<td>C3H/HeJ</td>
<td>0.33 ± 0.13</td>
<td>2.23 ± 0.36</td>
</tr>
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* Levels were determined by ELISA for mouse sera from different strains of mice at various times after infection.

TABLE 4. Effect of immunization with H. felis sonicate plus CT on challenge with viable H. felis in C3H/He and C3H/HeJ mice

<table>
<thead>
<tr>
<th>Immunization group</th>
<th>C3H/He mice</th>
<th>C3H/HeJ mice</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Urease</td>
<td>Histology</td>
</tr>
<tr>
<td>PBS control</td>
<td>9/10 (90)</td>
<td>8/9 (89)</td>
</tr>
<tr>
<td>H. felis + CT</td>
<td>2/20 (10)</td>
<td>3/20 (15)</td>
</tr>
</tbody>
</table>

* Numbers and percentages of mice infected with H. felis 3 weeks after oral challenge of immunized and control C3H/He and C3H/HeJ mice.

† Significantly lower level of H. felis colonization than that of the control animals ($P < 0.001$ by the $\chi^2$ test).
utes to the tissue damage seen in the stomach. This response is probably focused against the proliferative zone of the body mucosa, such that differentiation into parietal cells and chief cells is prevented and mucus metaplasia occurs (16). Gamma interferon is the signature cytokine produced by Th1 cells, and it is well known that LPS treatment of mice results in the rapid appearance in serum of a factor which induces gamma interferon production (18). This activity was identified as IL-12, a cytokine produced by phagocytic cells, particularly macrophages.

LPS exposure of macrophages to LPS-endotoxin often makes them refractory to endotoxin-induced effects such as TNF-α secretion following a second exposure. This tolerance to the effects of endotoxin is partially due to the production of nitric oxide as a result of the primary LPS exposure (9). However, not all LPSs can induce this refractory state, and it is tempting to speculate that the LPSs from Helicobacter species may continually activate macrophages in C3H/He mice over prolonged periods, thereby contributing to chronic gastritis. Whether this immunoreactivity against the gastric tissue is a consequence of bystander damage or is due to activation of T cells with a specificity against gastric tissue is unknown. The working hypothesis of our group is that these phenomena in our mouse model represent one manifestation of gastritis in humans which is independent or possibly additive to the effects of IL-8-driven active chronic gastritis.

The Mohammadi study also investigated the cell phenotype of inflammation that was associated with oral immunization and challenge with living H. felis. They demonstrated a Th1-type phenotype of immunization-associated gastritis but also showed the presence of IL-4-producing cells, indicating the induction of a Th2-type response (16). The immunization studies reported here show that the capacity to induce a Th1 response, as evidenced by the presence of host-dependent gastritis in C3H/He mice, is independent of the protective response which has been suggested to be due to Th2-driven immunity. This has important ramifications with respect to the safety of future H. pylori vaccines.

The clear-cut distinction with respect to Helicobacter-induced gastritis in C3H/He compared to C3H/HeJ mice provides an extremely good model to further investigate the exact mechanisms of host-dependent gastritis. We believe that this understanding of H. pylori-associated atrophy in human populations will provide insight into factors that lead to the induction of gastric adenocarcinoma in some individuals and populations.

ACKNOWLEDGMENTS

This work was supported by a grant from the National Health and Medical Research Council, Canberra, Australia. T. Sakagami was funded through the Vehara Foundation Scholarship of the Taisho Foundation.

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Editor: R. E. McCallum


