Mice Carrying a Truncated Apc Gene Have Diminished Gastric Epithelial Proliferation, Gastric Inflammation, and Humoral Immunity in Response to Helicobacter felis Infection

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ABSTRACT

Helicobacter pylori infection and adenomatous polyposis coli (Apc) gene mutations have been linked to gastric cancer in humans, but possible synergistic interaction(s) between these risk factors have not been examined. Fourteen C57BL/6 wild-type and 14 Apc1638 heterozygous mice were inoculated with Helicobacter felis at 6 weeks of age and compared at various time points with a similar number of uninfected control mice of the same genotype. Both infected and uninfected Apc1638 mice had a limited incidence of atypical proliferation foci in the mucosa of the antrum and pyloric junction at 4.5 and 6 months of age, whereas polyps of the antrum and pylorus were present in all mice, regardless of infection status, at 7.5 months. In contrast, no altered gastric mucosal foci were observed in control or infected C57BL/6 mice at any time point. Interestingly, the infected Apc1638 mice had less epithelial proliferation and inflammation in the body of the stomach, lower anti-H. felis serum IgG antibody responses (although both the wild-type and Apc mutant mice had a Th1-like immune response, based on a predominantly IgG2a immunoglobulin response), and higher bacteria and urease scores than did infected wild-type C57BL/6 mice. In conclusion, the Apc1638 truncating mutation leads to gastric dysplasia and polyposis of the antrum and pyloric junction, but H. felis infection of the Apc mutant mouse does not lead to an increased rate of gastric neoplasia. In addition, our data suggest this Apc mutation may actually lead to decreased immune, inflammatory, and gastric hyperplastic responses to Helicobacter infection, suggesting the possibility of a novel role for this tumor suppressor gene in the immune and local tissue responses to gastric bacterial infection.

INTRODUCTION

The pathogenesis of gastric cancer, like that of many tumors, involves a complex interplay of environmental and genetic factors (1). Over the last decade, several studies strongly supported the hypothesis that infection with the gastric bacterium Helicobacter pylori represents an important carcinogenic risk factor, but the underlying mechanisms that are involved have not been elucidated (2). Studies from our laboratory using a mouse model of Helicobacter felis infection suggest that chronic Helicobacter infection leads to an increased proliferative rate in the gastric mucosa, and this increased proliferation may be associated with increased risk of cancer formation (3). However, because the majority of individuals infected with H. pylori do not develop gastric cancer, it is clear that H. pylori infection is not wholly responsible for the process of malignant transformation.

The recognition of "familial gastric cancer" has suggested the presence of genes that may predispose individuals to the development of gastric cancer (4–7). A number of alterations in tumor suppressor genes have been described in sporadic gastric cancer, including the loss of heterozygosity at the Apc, DCC, and p53 loci (8–10). LOH at the p53 locus represents the most common genetic alteration and has been reported in 60–70% of specimens (1). Recent studies from our laboratory showed that C57BL/6 mice lacking one copy of the p53 gene and infected with H. felis developed gastric adenomatous lesions with a higher proliferative index than that of wild-type mice but did not appear at higher risk for overt gastric cancer in mice up to 1 year old (11).

Mutations in the Apc gene are found in the earliest stages of colorectal carcinogenesis and are thought to play a crucial role in the development of adenomatous polyps, which then progress to cancer (11). Germline mutations in the Apc gene are responsible for the syndrome known as FAP, which is an autosomal dominant disorder that is characterized by the formation of hundreds to thousands of colonic polyps and a high likelihood of colon carcinoma (12, 13). Gastric polyps or cancers are occasionally seen in FAP patients, and the risk of gastric cancer in FAP patients has been estimated to be 7–10-fold higher than in the general population (14, 15). Nevertheless, the overall importance of Apc mutations in gastric cancer remains uncertain.

Furthermore, it remains unknown whether a genetic event such as an Apc mutation represents an independent pathway for gastric carcinogenesis or predisposes an individual to accelerated carcinogenesis in the presence of Helicobacter infection. Several different lines of mice carrying mutations in the Apc gene have been described (16, 17). One of these Apc mutations (Apc1638) was shown to lead to colonic polyposis and tumors of the small intestine. In older mice, gastric tumors were occasionally observed, although the time course was not well characterized (16). Therefore, we undertook a detailed examination of the gastric histology of Apc1638 mice on a C57BL/6 background, in the presence or absence of H. felis infection, and compared these results with wild-type mice treated in a similar manner. These studies suggest that H. felis infection of Apc1638 mice does not significantly increase the risk of gastric neoplasia. Interestingly, the H. felis-infected Apc mutant mouse developed less gastritis, less epithelial metaplasia and proliferation in the body of the stomach, and lower IgG immune response to H. felis (statistically significant; P < 0.01) than did H. felis-infected wild-type mice. These data suggest a novel role of the Apc gene in immune and local tissue responses to gastric bacterial infection.

MATERIALS AND METHODS

Animals. Twenty-eight 4-week-old heterozygous Apc1638 and 28 6-week-old C57BL/6 wild-type mice were used in the study. As previously reported, the Apc1638 mice develop spontaneous intestinal and colonic polyps and colon cancer (16). They were originally generated in the C57BL/6 background, but have been back-crossed for more than six generations into an inbred C57BL/6 background. The mice were all maintained in an Association for Assessment and Accreditation of Laboratory Animal Care-approved facility

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3 The abbreviations used are: LOH, loss of heterozygosity; Apc, adenomatous polyposis coli; FAP, familial adenomatous polyposis.

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Bacteria were harvested, aliquoted at a titer of $10^{10}$ organisms/ml in brain-heart infusion broth with 30% glycerol, and stored at $-70^\circ$C. Before use, aliquots were thawed, analyzed for motility, and cultured for evidence of aerobic or anaerobic microbial contamination.

**Experimental Infection.** Of the 28 Apc1638 heterozygous mice and 28 C57BL/6 wild-type mice, 14 of each genotype were inoculated with *H. felis*, and the other 14 of each genotype remained as uninfected controls. Inocula ($10^8$ bacteria in 0.5 ml) were delivered by gastric intubation into each test mouse three times at 2-day intervals by using a sterile oral catheter. At 3, 4.5, and 6 months postinfection, infected and uninfected mice (ages 4.5, 6, and 7.5 months, respectively) were killed with CO$_2$ and necropsied (Table I).

**Histological Evaluation.** At necropsy, the stomach was removed *en bloc* and opened, the food was removed, and the presence or absence of polyps was grossly assessed. The tissue that was grossly examined consisted of the gastric mucosa, beginning at the gastroesophageal junction and ending just beyond the gastroduodenal junction. Stomach tissues were then fixed in neutral buffered 10% formalin, processed by standard methods, embedded in paraffin, sectioned at 5 $\mu$m, and stained with H&E and Warthin-Starry. The glandular mucosa of the body, antrum, and pylorus were histologically examined for polyps, as well as a number of inflammatory and epithelial changes. The degrees of inflammation and proliferation were assessed qualitatively by microscopic evaluation and comparison. The sections were also assessed for the presence of *H. felis* and the degree of bacterial colonization. The small intestine, cecum, and colon were separated at necropsy. The tissues were

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**Table 1** Frequency of gross polyps and microscopically observed, dysplastic, or adenomatous foci in the gastric antrum or pylorus of Apc1638 mice

<table>
<thead>
<tr>
<th>Mice</th>
<th>No. of animals</th>
<th>Polyp</th>
<th>Dysplasia</th>
<th>Adenoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.5 mo old (n = 4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apc + <em>H. felis</em></td>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Apc control</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 mo old (n = 4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apc + <em>H. felis</em></td>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Apc control</td>
<td>2</td>
<td></td>
<td>1</td>
<td>2 (2)</td>
</tr>
<tr>
<td>7.5 mo old (n = 6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apc + <em>H. felis</em></td>
<td>6</td>
<td>11 (6)</td>
<td>3 (3)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Apc control</td>
<td>6</td>
<td>10 (5)</td>
<td>1</td>
<td>6 (5)</td>
</tr>
</tbody>
</table>

- Total number of animals in group with either gross or microscopic lesions.
- Number of foci, number of animals affected in parentheses.
- None recorded.

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**Fig. 1.** Fundic mucosal changes and inflammation associated with *Helicobacter felis* infection in Apc1638 and wild-type C57BL/6 mice (6 months postinfection). Control Apc1638 (a) and control C57BL/6 (b) mice have normal fundic architecture and an absence of inflammatory infiltration. c. *H. felis*-infected Apc1638 mice have typically limited hyperplasia and otherwise unmodified fundic mucosal architecture, with limited inflammation. There is focal lymphocytic infiltration in the submucosa at the junction of the nonglandular and glandular regions. d. the most intense gastric lesions were observed in the fundus of C57BL/6 mice infected with *H. felis*. There is marked submucosal infiltration by lymphocytes and a mixed multifocal inflammatory infiltrate in the mucosa. The fundic mucosa is hyperplastic, with extensive attrition of parietal cells and replacement of the deep fundic glandular epithelium by mucus epithelium. Staining, H&E. Scale bar, 200 $\mu$m.
Apc1638 (Apc knockout) mice were inoculated with *H. felis* or with control broth at 6 weeks of age, and then they were sacrificed at ages 4.5 months (3 months postinoculation), 6 months (4.5 months postinoculation), or 7.5 months (6 months postinoculation) and evaluated. In the *H. felis*-infected C57BL/6 wild-type mice, mild mucosal thickening of the stomach was observed at 4.5 months of age, which progressed to moderate gastric hypertrophy by 7.5 months. No gastric cancers or polyps were observed in the C57BL/6 wild-type mice. The gross and histological findings from infected and uninfected Apc mice are summarized in Table 1. In the Apc1638 mice, no gross polyps or gastric thickening or hypertrophy were evident at the first two time points (4.5 or 6 months). However, by the age of 7.5 months, gastric polyps were observed in six of six uninfected Apc1638 mice and in six of six infected Apc1638 mice. Polyps were typically localized in the pyloric region.

**Apc1638 Mice Demonstrate Decreased Fundic Histological Alterations in Response to *H. felis* Infection.** C57BL/6 mice that were infected with *H. felis* for 3, 4.5, and 6 months (ages 4.5, 6, and 7.5 months, respectively) had distinctive gastric lesions, primarily affecting the pyloric fundic mucosa and submucosa. These lesions were greater in intensity than changes observed in other experimental groups. By 7.5 months of age, the fundic mucosa changes had progressed from moderate to marked, multifocal hyperplasia of the pyloric mucosa and metaplastic replacement of chief cells of the fundic glandular epithelium (Fig. 1d). There was also moderate-to-marked loss of the pyloric cells and dilation of the fundic glands in these mucosa regions, which increased in intensity over time. Foci of abnormal eosinophilic columnar epithelial cells were frequently present among the hyperplastic mucous glands of the fundus. The antral mucosa was less severely affected and demonstrated only moderate thickening of the pyloric glands (Fig. 2).

In contrast to the C57BL/6 mice, the Apc1638 mice infected with *H. felis* had mild hyperplasia of the fundic mucosa but generally lacked the morphological alterations of the fundic glandular epithelium (Fig. 1c). Mucous neck cell hyperplasia with chief cell replacement and mild pyloric cell attrition were observed infrequently. The control Apc and the control C57BL/6 mice, although typically normal (Fig. 1, a and b), also had infrequent foci of mucus cell hyperplasia in the pyloric fundic mucosa that were associated with variable pyloric cell attrition and local mild-to-moderate granulocytic infiltration of the lamina propria. In the antral mucosa, mild-to-moderate hyperplasia was observed at 6 months postinoculation in the infected Apc1638 mice and was often associated with foci of dysplasia and adenomatous growth in the antral mucosa at the pyloric junction (Fig. 3). However, similar findings were also observed in the control Apc1638 mice. Foci

Fig. 2. C57BL/6 mice infected with *H. felis* have moderate hyperplasia and inflammation of the antral mucosa (6 months postinfection). The lamina propria and submucosa contain multifocal lymphoplasmacytic and neutrophilic infiltrates. The glands of the antral mucosa are lengthened and mildly dilated. Staining, H&E. Scale bar, 100 μm.

Fig. 3. Papillary adenoma at the pylorus in an Apc1638 mice (7.5 months of age). This mouse was a control mouse; however, similar lesions were observed in *H. felis*-infected Apc1638 mice. This was the most common form of gastric neoplasm noted in this study. Staining, H&E. Scale bar, 500 μm.

**RESULTS**

*Apc1638 Mutation Leads to Gastric Polyp Formation in Both Infected and Uninfected Mice.* The C57BL/6 (wild type) and Apc1638 (Apc knockout) mice were inoculated with *H. felis* or with control broth at 6 weeks of age, and then they were sacrificed at ages 4.5 months (3 months postinoculation), 6 months (4.5 months postinoculation), or 7.5 months (6 months postinoculation) and evaluated.
of atypical mucosal proliferation in the antrum and pylorus were rarely seen at the 4.5-month time point but were frequently seen in control and infected Apc mice at the latter two time points (Table 1). Focal dysplasia or adenomatous growth in the antral mucosa or at the pyloric junction were observed in most of the control and infected Apc mice at 7.5 months of age. Similar dysplastic and adenomatous foci were not observed in control or infected C57BL/6 mice at any time point.

Apc1638 Mice Demonstrate Decreased Inflammatory Responses and Increased Bacterial Counts after H. felis Infection.

The C57BL/6 mice showed intense inflammatory responses after H. felis infection. The prominent fundic epithelial changes in this group were accompanied by moderate-to-severe lymphocytic inflammation of the mucosa and submucosa (Fig. 1d). The lymphocytic infiltrate was occasionally organized into multiple discrete aggregates within the superficial mucosa. There was also moderate-to-severe neutrophilic inflammation of the fundic lamina propria and submucosa in several mice. The antral mucosa often had mild-to-moderate infiltration by neutrophils and lymphocytes (Fig. 2).

The Apc1638 mice, on the other hand, generally lacked the inflammatory changes of the fundic glandular epithelium. The fundic inflammation was primarily limited to localized submucosal aggregates at the junction with the nonglandular region (Fig. 1c). Mucosal inflammation was typically inapparent to mild, although one mouse had a moderate lymphoid infiltrate within the fundic mucosa at 3 months postinfection. Mild-to-moderate lymphoid inflammation in the antral mucosa was commonly associated with focal dysplasia and adenomatous proliferation of the antrum and pylorus; however, less proliferative regions of the antrum had only inapparent-to-mild inflammation.

In the H. felis-infected C57BL/6 mice, Warthin-Starry-stained sections of gastric mucosa showed bacteria that are morphologically consistent with H. felis, but these bacteria were present in low numbers within the glandular crypts of the fundic mucosa and were rarely observed in the antral mucosa (Fig. 4b). In contrast, in the Apc1638 mice, dense clumps of bacteria morphologically consistent with H. felis were commonly observed in the glandular crypts of the fundic and antral mucosa (Fig. 4a). Although colonization was high in both regions, the antral mucosa appeared to be more densely colonized than the fundic mucosa.

![Graph of serum IgG response to H. felis](image)

**Fig. 5.** Decreased serum IgG antibody responses to *H. felis* in Apc1638 mice, compared to wild-type mice. Serum IgG titer in response to *H. felis* antigen was measured by ELISA (see “Materials and Methods”). The humoral responses of the C57BL/6 mice were greater than those of the Apc knockout mice at all time points (*P* < 0.05).
Table 2 IgG2a response to Helicobacter felis

<table>
<thead>
<tr>
<th>Strain</th>
<th>Infection status</th>
<th>Optical density* (mean ± SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C57BL/6+</td>
<td>3 mo&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.17 ± 0.13 (4) 1.67 ± 0.15 (4) 1.12 ± 0.21 (6)</td>
</tr>
<tr>
<td>Apc+</td>
<td>3 mo&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.12 ± 0.07 (4) 0.15 ± 0.06 (4) 0.20 ± 0.11 (6)</td>
</tr>
<tr>
<td></td>
<td>6 mo&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.00 ± 0.00 (4) 0.00 ± 0.00 (4) 0.01 ± 0.00 (5)</td>
</tr>
</tbody>
</table>

* Serum IgG subtype class was determined by ELISA (see “Materials and Methods”). Both strains of mice developed a humoral response predominantly consisting of an IgG2a response, which is consistent with a Th1-like immune response to Helicobacter. The C57BL/6 response was significantly greater at all time points (P < 0.05). An IgG1 response to H. felis was undetectable in all mice.

DISCUSSION

Apc1638 Mice Show Decreased Specific Antibody Responses to H. felis Infection. The IgG responses of the H. felis-infected C57BL/6 mice were significantly greater than the responses of the Apc1638 mice at each time point (Fig. 5; P < 0.05). The humoral response of C57BL/6 mice increased over the first 4 months postinfection, before the response plateaued at 18–26 weeks. In contrast, the IgG responses of the Apc1638 mice were consistently lower and not progressive in magnitude over time, despite persistent infection.

The serum IgG subisotype formed by the C57BL/6 mice in response to persistent H. felis infection was predominantly IgG2a, consistent with a Th1-like T-cell response, as has been reported (Ref. 21; Table 2). IgG1, associated with Th2-like immune responses, was undetectable (data not shown). The infected Apc1638 mice also predominantly produced IgG2a and, therefore, also responded to H. felis antigens with a Th1-like response. Similar to the low and unchanging magnitude of the total IgG response to H. felis, the IgG2a responses of the Apc1638 mice were significantly lower than the responses of the C57BL/6 mice at all time points (P < 0.05).

Gastric Urease. The rapidity of positive color development (i.e., time elapsed in hours before the urease reagent turns pink) in the gastric mucosa is proportional to the density of colonization by urease-positive H. felis (19, 22). The rapid positive urease scores, in relative terms, in H. felis-infected Apc mutant mice indicated consistently higher H. felis colonization compared to that of C57BL/6-infected wild-type mice (Fig. 6). This difference in H. felis colonization measured by rapidity of urease positivity between the two groups of mice was recorded at each time point (3, 4.5, and 6 months postinoculation) of the study. At 3 months, all of the Apc mice had positive urease scores by 12 h, with seven mice heavily colonized with H. felis, as indicated by positive urease scores being recorded within 2–3 h. However, only 50% of the C57BL/6-infected mice had positive urease scores in gastric biopsies within the 12-h period. This assay correlated well with the numbers of H. felis observed semiquantitatively in the infected Apc C57BL/6 wild-type mice by histological examination of Warthin-Starry-stained gastric tissue.

Although a number of studies have indicated that Apc may function as the “gatekeeper” of colonic epithelial proliferation and that mutation in the Apc gene is critical in the pathogenesis of colorectal carcinoma (23), the possible role of Apc in the pathogenesis of gastric cancer is not understood. Several reports have described LOH at the 5q locus in up to 30–40% of gastric cancers (8–10). One of the targets in 5q LOH may well be the Apc gene on 5q21. Therefore, we decided to study the Apc1638 mice (16) to characterize the effect of this mutation on the gastric epithelium on H. felis-infected and uninfected mice.

In the initial description, Apc1638 mice progressively developed colonic polyps, intestinal adenomas, and adenocarcinomas (16). Here, we show that the Apc1638 mutation leads to gastric polyph formation in mice, with the initial gross polyphs detected at 7.5 months of age. The polyphs were predominantly found in the pyloric region, whereas the fundic region of the stomach seemed to remain uninvolved. Because the Apc1638 mice begin to die at 8 months of age from colon carcinoma (16), our study was not extended beyond this time point. Nevertheless, it appears that a mutation in the Apc gene leads to a similar phenotype in the stomach as that seen in the colon, although the time course in the stomach is significantly delayed.

A previous report indicated that gastric cancer did occur in 1 of 11 Apc1638 mice examined at 1 year of age (16). This finding prompted us to examine the possibility that Helicobacter infection, a known environmental risk factor for gastric cancer, might accelerate this process. Grossly observable polyps and microscopic foci of dysplasia and adenomatous growth were observed in the stomachs of uninfected and infected Apc mice. However, the incidence of these gross and histological lesions were similar regardless of infection status. Pro-
gression to gastric carcinoma was not observed in either group. These observations suggest that Helicobacter infection did not exacerbate the incidence or progression of dysplastic and adenomatous gastric lesions associated with the Apc mutation over the time period examined. We previously observed a possible additive effect between Helicobacter infection and a heterozygous mutation in the p53 gene in mice examined 1 year post-H. felis infection (3). Overall, our results suggest that Helicobacter infection may represent a separate pathway for gastric cancer pathogenesis, independent of Ape mutation. In fact, the incidence of 5q LOH is much higher than that of mutations in the Apc gene (1-20%; Refs. 24-27), raising the possibility that tumor suppressor genes other than Apc may be important in gastric cancer. MCC is one tumor suppressor gene that is closely linked to Apc, and a recent report suggests the possibility of other tumor suppressor genes on this chromosomal region (27).

Perhaps the most surprising result was that the combination of Helicobacter infection and the Apc1638 mutation actually resulted in an inhibition of the proliferative response to Helicobacter in the fundic mucosa. Thus, although the wild-type C57BL/6 mice showed a marked expansion of the gastric mucus neck cells (and a concurrent loss of parietal and chief cells), resulting in an overall thickening of the gastric mucosa, the Apc1638 mice showed a reduced amount of these changes. Instead, the gastric mucosa of the Helicobacter-infected Apc1638 mice had limited proliferation and, in some cases, appeared similar to that of uninfected wild-type C57BL/6 mice.

The lack of a hyperplastic response to Helicobacter infection in the Apc1638 mice was closely paralleled by the lack of a significant local inflammatory response. The marked infiltration of the gastric mucosa by mononuclear and polymorphonuclear leukocyte inflammatory cells that was observed in the Helicobacter-infected C57BL/6 mice was not observed in the Helicobacter-infected Apc1638 mice. This finding supports previous studies that have suggested a close correlation between the magnitude of cellular proliferation and the severity of gastric inflammation in response to Helicobacter that is observed in a number of different mouse strains (28). In addition, the Apc1638 mice consistently showed a decreased systemic IgG immune response to Helicobacter infection, with a 6-fold reduction in antibody titers observed at 20-26 weeks postinoculation. It appears that the Apc mice and wild-type C57BL/6 both respond with a Th1-like T-cell response, albeit at a lower magnitude in the Apc mouse. A Th1 response has been associated with the significant gastritis noted in some humans infected with Helicobacter pylori (29) and in the Helicobacter mouse model (21). The difference in magnitude of both the total IgG and IgG2a subclass response is, therefore, consistent with the marked difference between the inbred mouse strains in gastric inflammation scores. Although a lower density of bacterial infection might account for the finding of lower antibody titers, this possibility was excluded by the demonstration of equal or greater numbers of bacteria or urease activity measured in the Apc1638 mice compared to the wild type. Thus, overall, the Apc1638 mice demonstrated higher bacterial loads and urease counts, along with decreased antibody, inflammatory, and proliferative responses. Because the Apc1638 mice differ from the wild-type C57BL/6 mice only in the single genetic locus, it seems reasonable to conclude that the Apc1638 mutation is responsible for both the decreased immune response and the increased bacterial colonization observed after Helicobacter inoculation.

In response to infection of the gastric mucosa with Helicobacter, the C57BL/6 mice developed a significantly greater humoral titer than did the Apc1638 mice. This greater antibody response was associated with a more severe inflammatory response and may have contributed to inhibition of Helicobacter colonization. Both systemic IgG and mucosal IgA have been shown to be protective against colonization of mice with Helicobacter (30, 31). The low titer developed by the Apc1638 mice, when correlated with lower inflammatory scores and the presence of increased bacterial colonization, as evidenced by both higher bacterial colony counts and urease scores, suggests a potential defect in the ability of the Apc mutant mouse to respond immunologically to an antigenic challenge at the mucosal surface. Although there has been no documentation, to our knowledge, that the Apc1638 mouse has an immune deficiency or difficulty with opportunistic infections, the observations made in this study may be the first evidence that this mouse strain has a deficiency either in the inflammatory cascade or in antigen processing and presentation at the mucosal surface. Defect(s) in the inflammatory response would result in less recruitment of antigen-processing cells to the gastric mucosa and associated lower tissue cytokine levels, resulting in less amplification of the immune response through autocrine and paracrine cellular effects (32).

The exact function of the Apc gene product has remained elusive. It is likely that Apc plays a role in cellular adhesion through interactions with @-catenin and possibly functions in signal transduction through associations with the Tcfl family of transcription factors (33). Apc-catenin complexes are believed to exist in a dynamic equilibrium with catenin-E-cadherin complexes and pools of free catenins within cells. Mutation in the Apc gene product might affect its interaction with @-catenin in such a way that would alter the availability of catenins to enter other compartments. A role for E-cadherin in the immune response to bacteria was recently suggested by experiments involving expression of a dominant negative N-cadherin lacking an extracellular domain (NCADΔ) in the intestinal villi of mice (34). Mice that expressed the NCADΔ only in their villus enterocytes had clusters of bacteria infiltrating between poorly adherent intestinal cells, but these mice showed only a limited mucosal immune response, suggesting that their immune response was in some way suppressed by the NCADΔ (34). Our findings support this model of the Apc-catenin-E-cadherin pathway playing a central role in gastrointestinal immunity. Although the exact mechanism at this time remains unclear, our study suggests further investigation of the role of Apc in regulating the immune response to mucosal infection.

REFERENCES


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