Innate Immune Inflammatory Response against Enteric Bacteria Helicobacter hepaticus Induces Mammary Adenocarcinoma in Mice

Varada P. Rao, Theofilos Poutahidis, Zhongming Ge, Prashant R. Nambiar, Chakib Boussahmain, Yan Yan Wang, Bruce H. Horwitz, James G. Fox, and Susan E. Erdman

Division of Comparative Medicine, Massachusetts Institute of Technology, Cambridge, Massachusetts; Immunology Research Division, Department of Pathology, Brigham and Women's Hospital; Division of Emergency Medicine, Children's Hospital, Boston, Massachusetts; and Laboratory of Pathology, Faculty of Veterinary Medicine, Aristotle University of Thessaloniki, Thessaloniki, Greece

Abstract

Inflammation associated with bacterial infections is a risk factor for cancers in humans, yet its role in breast cancer remains poorly understood. We have previously shown that innate immune inflammatory response against intestinal bacteria is sufficient to induce colon cancer. Here we report that infecting Rag2-deficient C57BL/6 ApcMin/+ mice with an intestinal bacterial pathogen, Helicobacter hepaticus, significantly promotes mammary carcinoma in females and enhances intestinal adenoma multiplicity by a tumor necrosis factor α (TNFα)–dependent mechanism. The mammary and intestinal tumor development as well as the increase in proinflammatory mediators is suppressed by adoptive transfer of interleukin 10 (IL-10)–competent TR cells (14). Despite their high predilection for intestinal tumors, unmanipulated C57BL/6 ApcMin/+ mice rarely show mammary tumors when housed in our specific pathogen-free animal facilities (15), in contrast to higher tumor incidence reported previously in other animal facilities (13, 16). We reasoned that inflammation induced in the gut by proinflammatory microbial infection could have systemic effects, which would then influence carcinogenic events in other organs including mammary gland. Here, we investigate whether Helicobacter hepaticus–triggered inflammatory responses modulate carcinogenesis in ApcMin/+ mice, using a widely applied adoptive T-cell transfer model (17) and recombination-activating gene 2 (Rag2)–deficient ApcMin/+ mice, and assess the roles for innate immune inflammatory response in mammary and intestinal tumor development.

Introduction

Chronic inflammation promotes carcinogenesis and predisposes susceptible individuals to cancer (1, 2). In humans, infectious inflammation associated with prolonged activation of the host immune system by parasitic, viral, and bacterial agents has been shown to contribute to tumor formation at several sites including bladder (3), liver (4), and stomach (5). Similarly, inflammation of noninfectious nature has been associated with other types of cancer including colorectal cancer (6), lung cancer (7), and cancer of esophageal/gastric junction (8). Breast cancer, the most frequently diagnosed cancer in North America, nearly thrice its rate in the developing world, has increasing incidence rate at ~ 4% per annum over the past decade (9). Despite intense efforts to understand etiopathogenesis of breast cancer, no clear explanation for its increasing incidence has been forthcoming.

Cancers of bowel (10) and breast (11) have been associated with mutations in adenosomatosis polyposis coli (APC), the gene responsible for multiple intestinal neoplasia in humans and mice (12). Mice heterozygous for Apc gene (ApcMin+) develop a large number of intestinal polyps by 3 months of age (13) and this process has been shown to be inhibited by adoptive transfer of interleukin 10 (IL-10)–competent TR cells (14). Despite their high predilection for intestinal tumors, unmanipulated C57BL/6 ApcMin/+ mice rarely show mammary tumors when housed in our specific pathogen-free animal facilities (15), in contrast to higher tumor incidence reported previously in other animal facilities (13, 16). We reasoned that inflammation induced in the gut by proinflammatory microbial infection could have systemic effects, which would then influence carcinogenic events in other organs including mammary gland. Here, we investigate whether Helicobacter hepaticus–triggered inflammatory responses modulate carcinogenesis in ApcMin/+ mice, using a widely applied adoptive T-cell transfer model (17) and recombination-activating gene 2 (Rag2)–deficient ApcMin/+ mice, and assess the roles for innate immune inflammatory response in mammary and intestinal tumor development.

Materials and Methods

Experimental animals. All animals were housed in Association for Assessment and Accreditation of Laboratory Animal Care–approved facilities and maintained according to protocols approved by the Institutional Animal Care and Use Committee at Massachusetts Institute of Technology. ApcMin/+ mice on a C57BL/6J background were originally obtained from The Jackson Laboratory and bred in house as heterozygous ApcMin/+ wild type crosses to provide ApcMin/+ wild-type littermates for experimental recipients and donors. Before the study, Helicobacter-free status of the mice was confirmed by PCR using Helicobacter genus–specific primers as previously described (18). Experimental H. hepaticus infection. A total of 71 experimental mice were dosed at 2 to 3 months of age with H. hepaticus and housed separately in a bio-containment area within the same animal facility. H. hepaticus (strain 3B1, ATCC 51449; ref. 19) was grown under anaerobic conditions, prepared, and confirmed pure as described elsewhere (20). Experimental mice received 0.2 mL of fresh inoculum by gastric gavage every other day for a total of three doses. Cecum and colons were collected 3 to 4 weeks after the last dose.
postinfection at necropsy and analyzed by PCR using H. hepaticus–specific primers to confirm experimental infection (18).

Experimental design. A total of 20 female ApcMin/+ mice and 100 female Rag2−/− ApcMin/+ mice were included in various treatment regimens or as experimental controls. Some experiments were conducted using separate trials with four to eight mice each. Trials with statistically similar results were then combined for analyses.

Adoptive transfer of TcR cells. A total of 49 Rag2−/− ApcMin/+ mice, ages 3.5 to 4 months, were dosed with 3 × 106 wild-type TcR cells (N = 9), 3 × 106 IL-10−/− TcR cells (N = 8), or 1 × 106 wild-type TcR cells (N = 32 mice) 24 hours before H. hepaticus infection. CD4+/CD45RB+hCD25− (TcR) lymphocytes were isolated from spleen and mesenteric lymph nodes and adoptively transferred as previously described (14). The donor mice for TcR cells included male and female H. hepaticus–infected or Helicobacter-free C57BL/6 mice or H. hepaticus–infected IL-10-deficient C57BL/6 mice. The TcR-cell donors were dosed with H. hepaticus 8 weeks earlier. Experiments used in this study were all female mice, based on the earlier observation that mammary tumor incidence is greater in female mice (13). Repeat experiments were conducted with two or three groups of similar size for select experiments.

Tumor necrosis factor α neutralization. A total of 11 Rag2−/− ApcMin/+ mice, ages 3 to 4 months, infected with H. hepaticus, were treated 3-4 weeks later with anti–tumor necrosis factor α (TNFα) antibody (clone XT-3; BioExpress, West Lebanon, NH) at 200 µg per mouse thrice weekly for 1 week as previously described (15). Treated mice (N = 11) were compared with age-matched Rag2−/− ApcMin/+ mice that received sham antibody alone (N = 8). Neutralization of TNFα was confirmed by ELISA (not shown).

Treatment with IL-10-Ig fusion protein. A total of nine H. hepaticus–infected Rag2−/− ApcMin/+ mice, 3 to 4 months of age, were treated with IL-10-Ig fusion protein at 5 µg per mouse twice weekly (2-3 days apart) for 1 week. To produce the IL-10-Ig fusion protein, genes for murine IL-10 and immunoglobulin G2a (IgG2a) CH2 were fused and the chimeric gene was cloned into an adenoviral vector and the infectious cGMP-prepared virus was packaged in 293 cells. The virus was used to infect murine IL-10-deficient C57BL/6 mice. The transduced mice were dosed with IL-10-Ig fusion protein at 1 week as previously described (15). Treated mice (N = 11) were compared with age-matched Rag2−/− ApcMin/+ mice that received sham antibody alone (N = 8).

Results and Discussion

Innate immunity is sufficient for mammary and intestinal tumor development. Previously, we showed that the innate immune inflammatory response was sufficient to promote colo-rectal carcinoma in Rag2-deficient 129/SvEv mice (20, 22). In the present study, we first sought to determine whether lymphocytes are essential for mammary and intestinal tumorigenesis in ApcMin/+ mice. We find that unmanipulated Rag2−/− ApcMin/+ mice between 4 and 4.5 months of age develop significantly (P < 0.001) more frequent adenomas in the small bowel (Fig. 1A) when compared with age-matched ApcMin/+ controls housed under the same health status conditions. In addition, one Helicobacter-free Rag2−/− ApcMin/+ female mouse (1 of 16; 6%) developed a palpable mammary tumor. The findings of intestinal tumors and mammary tumors in Rag2−/− ApcMin/+ mice indicated that adaptive immunity is not required for tumorigenesis in the ApcMin/+ mouse model. Further, the development of significantly higher intestinal tumor multiplicity in Rag2−/− ApcMin/+ mice over their ApcMin/+ counterparts suggests that tumorigenesis is enhanced in the absence of lymphocytes. H. hepaticus infection promotes intestinal and mammary tumorigenesis. Because H. hepaticus infection has been shown to induce colonic cancer in 129 strain Rag2−/− mice devoid of lymphocytes (20), we asked whether infecting C57BL/6 Rag2−/− ApcMin/+ mice with H. hepaticus promotes intestinal and mammary tumor development. Four to six weeks after H. hepaticus infection, female Rag2−/− ApcMin/+ mice (N = 8) developed significantly (P < 0.001) greater multiplicity of intestinal polyps (μ = 110 ± 10.7; Figs. 1A and 2C) when compared with age-matched uninjected female control mice. Likewise, H. hepaticus–infected mice had significantly (P < 0.001) more frequent F4/80+ macrophages (12.6 ± 0.9 per high-power field) in the sections of intestines (Fig. 2G) when compared with those from H. hepaticus–free controls (4.8 ± 0.9 per high-power field), suggesting a role for these cells in pathogenesis. Interestingly, we find a significantly (P < 0.05) higher frequency of mammary tumors in H. hepatitis-infected Rag2−/− ApcMin/+ mice (7 of 15 mice; 43%; Figs. 1B and 2D) when compared with age-matched uninjected control female Rag2−/− ApcMin/+ mice. Adenosquamous mammary carcinoma in Helicobacter-infected Rag2−/− ApcMin/+ mice showed minimal squamous metaplasia (Fig. 2D) when compared with mammary tumors in ApcMin/+ mice promoted by proinflammatory CD4+/CD45RB+hCD25− TcR lymphocytes (15). In addition, mammary tumors of H. hepatitis–infected Rag2−/− ApcMin/+ mice had dense inflammatory infiltrates of F4/80+ macrophages (Fig. 2H), consistent with inflammation-associated breast cancer in humans (23, 24).

Similarly, we also find that ApcMin/+ mice (N = 11) infected with H. hepaticus showed an increase in the adenoma multiplicity in the small and large intestine (Fig. 1; Table 1) when compared with Helicobacter-free age-matched controls. In addition, 63% (7 of 11; P < 0.001) of female ApcMin/+ mice that received H. hepaticus 4 to 6 weeks earlier had palpably enlarged mammary glands (Fig. 1B) with histologic features of adenosquamous mammary carcinoma (Fig. 2B) when examined at 3 to 4 months of age. In contrast, no mammary tumors were found in Helicobacter-free ApcMin/+ females (0 of 8 animals) during the course of the study. Microscopically, the tumors in ApcMin/+ mice had more locally invasive borders and had increased squamation when compared with neoplastic mammary glands of Rag2−/− ApcMin/+ mice (compare Fig. 2B and D). Differences in histologic appearance of tumors may reflect adaptive immune-mediated alterations in the Wnt signaling pathway.
pathway (25). One explanation for the frequency of *H. hepaticus*–induced tumors in *ApcMin/+* may be the recently described immune deficits. Thymic atrophy and lymphopenia (26) may decrease TR cell competency in *ApcMin/+* mice, thereby enabling uncontrolled activation of *Helicobacter*-primed TR cells (27) or other cells of adaptive immunity, which may promote mammary and intestinal carcinogenesis. Nonetheless, the observation that *H. hepaticus* infection promotes mammary tumors in both lines of mice raises the likelihood that proinflammatory intestinal bacterial infections contribute to breast tumorigenesis in other mouse models as well as in women.

**H. hepaticus**–triggered intestinal and mammary carcinoma is TNFα dependent. To examine whether *H. hepaticus* infection is accompanied by up-regulation of proinflammatory cytokines, we analyzed gut mucosal expression levels of cytokines including TNFα, IL-12p40, IFNγ, and macrophage inflammatory protein 2 (MIP-2). We find increased expression of all four cytokines (Fig. 3) consistent with our prior findings in colitis and colon cancer (20). Because TNFα is a key cytokine implicated in inflammation-associated cancers (28), and treatment with anti-TNFα antibody has been shown to suppress polyp formation in *ApcMin/+* mice (15), we asked whether the *H. hepaticus*–promoted tumorigenesis in *Rag2−/−ApcMin/+* is dependent on TNFα. Indeed, neutralization of TNFα by antibody significantly suppressed both intestinal (*P* < 0.001) and mammary tumors (*P* < 0.05; Fig. 1A and B) in the *H. hepaticus*–infected *Rag2−/−ApcMin/+* mice. Therapeutic
effects of TNFα neutralizing antibody in these mice suggest that TNFα or its downstream signaling mediators are required to sustain intestinal and mammary tumors in this setting.

The underlying cellular and molecular mechanisms of mammary tumor promotion by *H. hepaticus* in Rag2−/−ApCo−/− mice need further study. Mammary tumors from *H. hepaticus*–infected Rag2−/−ApCo−/− mice show an 18-fold increase (*P < 0.0001*) in TNFα-gene expression when compared with mammary tissues of uninfected mice, indicating a localized inflammatory response. Tumorigenesis may be initiated by systemic increases in proinflammatory factors and/or by the trafficking of activated innate immune cells to target tissues. Another possibility is translocation of Helicobacter organisms or their antigens to mammary tissue in infected mice with attendant localized proinflammatory host response, which subsequently promotes development of mammary cancer. Taken together, these data indicate that *H. hepaticus*–triggered TNFα-mediated innate immune inflammatory response promotes epithelial tumorigenesis locally as well as in other sites such as mammary gland.

CD25+ regulatory T cells inhibit mammary and intestinal tumorigenesis. Prior studies have shown that CD25+ regulatory (TREG) cells are sufficient to prevent *H. hepaticus*–triggered colitis and colon cancer (20, 27). To determine whether TREG cells can inhibit Helicobacter–promoted tumorigenesis in Rag2−/−ApCo−/− mice, nine female mice, 2 to 3.5 months of age, were infected with *H. hepaticus* and adoptively transferred with 3 × 10^5 TREG cells per recipient of TR cells collected from Rag2−/−ApCo−/− mice. When examined 3 to 4 weeks later, we found a significant (*P < 0.001*) reduction in intestinal adenoma multiplicity (μ = 14.8 ± 3.69; Fig. IA) and observed no mammary tumors (*P < 0.05*) in these infected TR cell–recipient mice. Additionally, treatment of *H. hepaticus*–infected mice with TREG cells resulted in a significant (*P < 0.001*) decrease in the levels of intestinal mucosal proinflammatory cytokines including TNFα and MIP-2 (Fig. 3). These
data indicate that TR cells are sufficient to inhibit mammary and intestinal tumorigenesis in Rag2−/− ApcMin/+ mice. These findings match earlier data from our laboratory (14, 15) as well as by others (29) showing that TR cells are not only capable of suppressing intestinal adenoma multiplicity in recipients that were infected at least 8 weeks earlier with H. hepaticus, for adoptive transfer into H. hepaticus–infected IL-10-deficient syngeneic donors into uninfected recipients of IL-10-deficient TR cells (N = 8; μ = 100.4 ± 9.91) when compared with untreated control mice (N = 8; μ = 84.13 ± 4.7). These data showing no inhibitory effect on tumorigenesis by IL-10-deficient TR cells, even when the donors were microbially challenged, are consistent with our recent observations in this model (14) and parallel our earlier studies in 129/SvEv Rag2−/− mice showing no protection from colitis and colon cancer when TR cells donors lack IL-10 (20, 22).

**Prior challenge with H. hepaticus enhances antitumor potency of TR cells.** Microbes or microbial products enhance survival, proliferation, and cytokine production by TR cells (30). To test whether protective antitumor effects of TR cells can be enhanced by prior microbial challenge, we first determined a suboptimal dosage of 1 × 105 CD45RBloCD25+ wild-type TR cells per recipient (31). We then used this lower dose of TR cells derived from donors that were infected at least 8 weeks earlier with H. hepaticus, or alternatively from donors that remained uninfected, for adoptive transfer into Rag2−/− ApcMin/+ mice at time of infection with H. hepaticus. We found that TR cells isolated from H. hepaticus–exposed donors were significantly (P < 0.001) more effective at suppressing H. hepaticus–induced intestinal tumors when compared with cells from naive donors. It remains to be seen whether CD45RBloCD25+ TR cells, or other cell subsets with regulatory functions, act similarly as potent promoters of epithelial homeostasis after microbial challenges. Kullberg et al. (31) have previously shown that CD45RBloCD25+ TR cells from H. hepaticus–exposed mice were efficacious in protecting against H. hepaticus–induced TCR cell–mediated colitis. Studies in progress may reveal dynamics of immune tolerance involving both innate immunity and host TR cell competency.

To test whether the H. hepaticus–induced enhancement in antitumor potency of TR cells is limited to H. hepaticus–triggered tumors, the lower dosage of TR cells from H. hepaticus–infected as well as uninfected donors was transferred in parallel into Helicobacter–free Rag2−/− ApcMin/+ recipients. We find that H. hepaticus–experienced TR cells are significantly (P < 0.001) more potent compared with cells from naive donors (P < 0.05) at suppressing intestinal adenoma multiplicity in recipients that were not infected with H. hepaticus. The finding that tumor multiplicity is significantly inhibited by Helicobacter–challenged donor TR cells in all recipients irrespective of their Helicobacter status suggests that prior proinflammatory challenges broadly enhance antitumor potency of TR cells, even against tumors of unknown etiology.

In light of recent studies showing that probiotic intestinal bacteria (32) and parasite antigens (33) enhance IL-10 and the protective functions of TR cells, it will be interesting to examine whether these agents will affect antitumor potency of TR cells in our model.

**IL-10 is critical to suppress H. hepaticus–promoted tumorigenesis.** In murine models, CD4+CD25+ regulatory (T R) cells require anti-inflammatory cytokine IL-10 to inhibit inflammatory bowel disease (27, 31), colon cancer (20, 22), and intestinal polyposis (14). To determine whether IL-10 is dispensable in TR cells endowed with microbially enhanced antitumor potency, we did adoptive transfer of TR cells from H. hepaticus–infected IL-10-deficient syngeneic donors into uninfected Rag2−/− ApcMin/+ recipients of IL-10-deficient TR cells (N = 8; μ = 100.4 ± 9.91) when compared with untreated control mice (N = 8; μ = 84.13 ± 4.7). These data showing no inhibitory effect on tumorigenesis by IL-10-deficient TR cells, even when the donors were microbially challenged, are consistent with our recent observations in this model (14) and parallel our earlier studies in 129/SvEv Rag2−/− mice showing no protection from colitis and colon cancer when TR cells donors lack IL-10 (20, 22).

### Table 1. Comparison of intestinal tumor frequency between ApcMin/+ and Rag2−/− ApcMin/+ mice

<table>
<thead>
<tr>
<th>Group</th>
<th>Hh status</th>
<th>No. mice</th>
<th>Small intestine</th>
<th>Large intestine</th>
</tr>
</thead>
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<tr>
<td>ApcMin/+</td>
<td>−</td>
<td>9</td>
<td>37.89 ± 3.57a</td>
<td>0.5 ± 0.3d</td>
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<tr>
<td></td>
<td>+</td>
<td>11</td>
<td>67.73 ± 11.36b</td>
<td>2.5 ± 0.2d</td>
</tr>
<tr>
<td>Rag2−/− ApcMin/+</td>
<td>−</td>
<td>16</td>
<td>82.69 ± 4.38b</td>
<td>1.4 ± 0.3</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>15</td>
<td>104.7 ± 9.50b</td>
<td>2.7 ± 0.6</td>
</tr>
</tbody>
</table>

NOTE: Data sharing a superscript letter are significantly different from each other. a, b, and c, P < 0.05; d, P < 0.01; e, P < 0.001. Mouse were either uninfected or dosed with H. hepaticus (Hh) and tumor multiplicity in small and large intestine was quantitated as described in Materials and Methods. Total tumor numbers in small and large intestine were separately analyzed between groups by using unpaired t test with Welch’s correction using Prism 4.0 software as described in Materials and Methods.

### Figure 3. H. hepaticus infection induces up-regulation of proinflammatory cytokines in Rag2−/− ApcMin/+ mice.

The intestinal mucosal expression levels of cytokines mRNA from uninfected, H. hepaticus–infected, and H. hepaticus–infected and TR cell (3 × 105)–treated mice are presented. A, IL-12p40; B, TNF-α; C, IFN-γ; and D, MIP-2. Infection with H. hepaticus significantly increased gene expression of all four cytokines analyzed. Adoptive transfer of wild-type TR cells significantly decreased expression of IFN-γ (P < 0.05), TNF-α, and MIP-2 (both P < 0.001). Cytokine gene expression was analyzed by RTase protection and the intensity of the protected fragments was quantified after normalization to glyceraldehyde-3-phosphate dehydrogenase, which is used as internal control. Columns, mean relative mRNA expression for each cytokine from a group of six to eight mice; bars, SE. Data were analyzed and compared as described in Materials and Methods for statistical significance.
To determine whether exogenously administered IL-10 will inhibit mammary and intestinal tumors, we treated H. hepaticus–infected Rag2−/−/ApcMin/+ mice (N = 9) with IL-10-Ig fusion protein for 1 week. In all nine mice, we observed significantly (P < 0.001) fewer intestinal adenomas when compared with untreated infected control mice (Fig. 1A). Likewise, when compared with the untreated group, only one of nine animals in the IL-10-lg treated group had a mammary tumor (Fig. 1B). These data support that IL-10 is sufficient to suppress tumors in the absence of lymphocytes. Although the cellular and molecular mechanism(s) through which IL-10 inhibits carcinogenesis are not well understood (34), whether through suppression of inflammatory cytokines, promotion of epithelial homeostasis, or induction of tolerogenic dendritic cells, the in vivo inhibitory effect(s) of IL-10-lg on epithelial cancers in mice lacking lymphocytes is promising and may facilitate new studies in this area.

In summary, the study shows for the first time that an enteric microbial infection promotes cancer in the mammary gland. It is plausible that other proinflammatory bacteria including H. pylori also exert extraintestinal carcinogenic effects. Mammary tumor suppression by anti-inflammatory regimens in the present and prior study (15) matches the clinical and epidemiologic data on the protective effects of anti-inflammatory therapies in women with breast cancer. That the wild-type donor TcR cells inhibit intestinal and mammary tumors in ApcMin/+ and Rag2−/−/ApcMin/+ mice highlights the prophylactic potential of TcR cells in inflammation-associated cancers. The observation that TcR cells from bacterially challenged mice possess greater antitumor potency suggests that microbial challenges in early life may augment protection against the inflammation-associated maladies, including cancer, later in life. It is tempting to speculate that stringent hygiene practices may decrease competency in TR cells, which, when coupled with other risk factors, could contribute to increases in breast and other epithelial cancers in Western countries. Nevertheless, due to their anti-inflammatory functions and pivotal roles in epithelial homeostasis, future studies with TcR cells may offer important clues to the design of more effective treatment and prevention strategies for inflammation-associated cancers in humans.

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References


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