Listeria monocytogenes Promotes Tumor Growth via Tumor Cell Toll-Like Receptor 2 Signaling

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Materials and Methods

Mice and cell lines. BALB/c (H-2b) mice were purchased from the National Cancer Institute. The WT hepatocarcinoma H22 cell line (BALB/c background) and TLR2 and TLR4 knockdown H22 cell lines were grown in DMEM supplemented with 10% fetal bovine serum (FBS) and 4 mmol/L glutamine.

Preparation of Lm bacteria. Lm 10403S, a virulent strain (a gift from Dr, Hao Shen, University of Pennsylvania, Philadelphia, PA; ref. 15), was used throughout the study. The bacteria were grown in Brain Heart Infusion Broth (BD Biosciences) at 37°C for 16 h, washed repeatedly, suspended in PBS, and stored at −80°C until use.

Tumor growth experiment. H22 tumor cells (2 × 105) were inoculated s.c. to the left flank of BALB/c mice (n = 10 per group). Tumor growth was monitored every 5 days by palpation. The length (L) and width (W) of tumors were measured, and the volume of tumor (V) was determined by the following formula: V = (L × W2)/2.

In vivo depletion of natural killer cells or immunoregulatory cells. Natural killer (NK) cell in vivo depletion was referenced previous method (16) by i.p. injection of 50 μL of rabbit polyclonal antibody against asialo ganglioside-N-tetraosylceramide (AGM1; Wako Chemicals). CD4−CD25− regulatory T cell (Treg) was depleted in vivo by i.p. injection of 100 μL of anti-mouse CD25 antibody (PC61.5; ebioscience). Myeloid suppressor cells (MSC) were depleted in vivo by i.p. injection of 100 μL of anti-mouse Gr-1 antibody (RB6-8C5; ebioscience).

Cytotoxicity assay. Tumor cells (5 × 105) were infected by incubation with Lm [1 × 108 colony-forming unit (CFU)] for 2 h and then cultured with 5 μg/mL gentamicin (17). Two days later, a fraction of cells was lysed and inoculated on agar plate for Lm culture. The white colonies were counted for the identification of infection of tumor cells by Lm. The infected tumor cells, colonies/cells >1, were used as target cells for cytotoxicity assay.

Abstract

The contribution of bacterial infection to tumorigenesis is usually ascribed to infection-associated inflammation. An alternate view is that direct interaction of bacteria with tumor cells promotes tumor progression. Here, we show that the microenvironment of large tumors favors bacterial survival, which in turn directly accelerates tumor growth by activating tumor cell Toll-like receptors (TLR). Listeria monocytogenes (Lm) survives in the microenvironment of large but not small tumors, resulting in the promotion of tumor growth. Lm did not affect the percentage of regulatory T cells or myeloid suppressor cells in the tumor. Through TLR2 signaling, Lm activated mitogen-activated protein kinases and nuclear factor-κB in tumor cells, resulting in the increased production of nitric oxide and interleukin-6 and increased proliferation of tumor cells. All of these effects were abrogated by silencing of nitric oxide and interleukin-6 and increased proliferation of tumor cells. These findings provide a new insight into infection-associated tumorigenesis and illustrate the importance of antibiotic therapy to treat tumors with bacterial infiltration. [Cancer Res 2007;67(9):4346–52]

Introduction

Chronic infection by bacteria is recognized as a risk factor for tumorigenesis, and the underlying mechanism is ascribed to infection-induced inflammation (1–3). The inflammatory response is triggered by interaction between bacteria and Toll-like receptors (TLR) expressed on immune cells or local tissue (4, 5). Chronic inflammation promotes neoplastic cell growth, may contribute to neovascularization (6), and is proposed as an initiating factor in 15% of human tumors (7). Nevertheless, the use of bacterial vaccines for immunotherapy of tumors is being reexamined because bacterial vaccines might efficiently activate a durable and robust antitumor response (8, 9). In particular, Listeria monocytogenes (Lm), a Gram-positive facultative intracellular bacterium, is being developed as a cancer vaccine platform because it can induce a potent innate and adaptive response (10–12). Furthermore, virulence-attenuated strains of Lm have been confirmed to have the same antitumor capacity as wild-type (WT) Lm (13), which may lead to clinical trials in the future.

Although much attention in recent years has been paid to the interaction between host and pathogen, direct interaction between bacteria and tumor cells has been largely overlooked. It is still unclear how tumor-associated bacteria interact with tumor cells and how the consequences of such interactions influence tumor progression and immunotherapy. Given that the tumor-associated bacteria can come not only from infection but also from immunization with bacterial vaccines, it is important to study the effects of interaction between bacteria and tumor cells on the tumor. We previously reported that tumor cells express TLRs (14) and suggested a potential link between tumor-associated bacteria and tumor cells. In this study, we found that the direct injection of Lm into local tumors resulted in the promotion of tumor growth rather than inhibition. This effect was due to the activation of tumor cell TLR signaling by Lm. These findings emphasize that the presence of bacteria in the tumor can directly accelerate tumor growth and suggest that antibiotic therapy may be beneficial to the treatment of bacterial infection-associated cancer.
Mice received $2 \times 10^5$ CFU of live *Lm* by i.v. injection followed by the second i.v. injection of $4 \times 10^5$ CFU of live *Lm* 7 days later. The splenic T cells were isolated with T-cell enrichment column (R&D Systems) from control mice or *Lm*-vaccinated mice 7 days after the second injection with *Lm* and used as effectors.

Standard 4-h $^{3}^{1}Cr$ release assay was done. Briefly, target cells were labeled with Na$^{23}$CrO$_4$ (0.1 μCi/10$^5$ cells; Amersham Pharmacia Biotech) at 37°C for 1 h. After extensive washing, target cells were incubated with effectors at different E/T ratios in triplicate for 4 h at 37°C, and $^{3}Cr$ released (cpm) into the supernatants was measured in a gamma counter to calculate percentage specific release. The percentage specific lysis was calculated by the following formula: percentage lysis = 100 × (experimental release – spontaneous release) / (maximum release – spontaneous release).

**Flow cytometry.** H22 tumor cells (2 × 10$^5$) were inoculated s.c. to mice. On day 15, 1 × 10$^5$ CFU of live *Lm* were injected directly to tumor site. Ten days later, tumor tissues were removed and digested with collagenase and hyaluronidase and grinded to single cells. The leukocytes in tumor tissues were isolated using Lymphocyte Separation Medium (Cellgro). Both tumor-infiltrating leukocytes and the grinded splenocytes were stained with phycoerythrin-labeled anti-CD3, FITC-labeled anti-CD4, and allophycocyanin (APC)-labeled anti-CD25 for Treg analysis by flow cytometry. To analyze MSCs, single cells from tumor tissue or spleen were fractionated by centrifugation on a Percoll (Amersham Biosciences) density gradient as described (18). The cells in fraction 2 were stained with APC-labeled anti-Gr-1 and FITC-labeled anti-CD11b. All above antibodies and their isotype-matched monoclonal antibodies were purchased from eBioscience.

**Isolation of tumor cells from gastric carcinoma patients.** Human gastric cancer tissues were acquired from clinical operation and digested with collagenase and hyaluronidase and grinded to single cells. The leukocytes in tumor tissues were isolated using Lymphocyte Separation Medium (Cellgro). Both tumor-infiltrating leukocytes and the grinded splenocytes were stained with phycoerythrin-labeled anti-CD3, FITC-labeled anti-CD4, and allophycocyanin (APC)-labeled anti-CD25 for Treg analysis by flow cytometry. To analyze MSCs, single cells from tumor tissue or spleen were fractionated by centrifugation on a Percoll (Amersham Biosciences) density gradient as described (18). The cells in fraction 2 were stained with APC-labeled anti-Gr-1 and FITC-labeled anti-CD11b. All above antibodies and their isotype-matched monoclonal antibodies were purchased from eBioscience.

**Isolation and culture of *Helicobacter pylori*.** The gastric specimens from surgery were transported to the laboratory within 1 h. Three biopsy specimens from *Helicobacter pylori*-positive patients were homogenized and inoculated onto trypticase soy sheep blood agar medium (BD, Becton Dickinson Microbiology Systems) containing 10% CO$_2$ and 95% relative humidity. The prim, and 2.5 IU/mL polymyxin B and then incubated at 35°C for 18 h. The white colonies were isolated and identified by Gram-stained smear and positive oxidase, catalase, and urease tests.

**Tumor cell proliferation assay.** H22 cells were seeded in 96-well plate (5 × 10$^3$ per well) and treated with heat-killed *Lm* (1 × 10$^5$ CFU) for 48 h. The proliferation assay was done with 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) cell proliferation kit (Roche Diagnostics) according to the manufacturer's instructions. The proliferation of gastric carcinoma cells in the presence of *H. pylori* was determined by the same method with 5 × 10$^3$ of gastric carcinoma cells and 2 × 10$^7$ CFU of *H. pylori* per well. Before the addition of MTTI, cells were washed with warm culture medium by spinning the plate at 500 rpm for 1 min and then discarding the supernatant. This washing procedure was repeated thrice to avoid the possible influence of *H. pylori*.

**Quantification of *Lm* in tissues.** *Lm*-vaccinated mice were sacrificed. The spleen and tumor tissue from the mice were homogenized in 5 mL of sterile PBS. Homogenates (100 μL) were added to sterile Brain Heart Infusion (BHI) agar plate and incubated at 37°C for 18 h. The white colonies were counted.

**Western blot.** Cell lysates (30 μg of total protein) and pre-stained molecular weight markers were separated by SDS-PAGE followed by transfer onto nitrocellulose membranes. The membranes were blocked in TBS with 0.5% of Triton X-100 containing 5% nonfat milk and probed with various antibodies (1:1,000). After incubation with the secondary antibody conjugated with horseradish peroxidase, membranes were extensively washed, and the immunoreactivity was visualized by enhanced chemiluminescence (ECL) according to the manufacturer's protocol (ECL kit, Santa Cruz Biotechnology). All antibodies were purchased from Cell Signaling.

**Cell transfection and luciferase assay.** Nuclear factor-κB (NF-κB) activity in cells was detected with a NF-κB-luciferase reporter vector (pSV40B-Luc). The NF-κB–binding sites in the vector consist of four concanamers of the synthetic oligonucleotide 5′-CTATGAGGACATTC-GACCTGGAGACTTCCACACCT-3′, each of which contains two NF-κB–binding sites derived from SV40 virus. The sequence encoding for firefly luciferase is controlled by eight NF-κB–binding sites and a synthetic basal TATA element. H22 cells (1 × 10$^5$) were transiently transfected with pSV40B-Luc (stored at laboratory) with LipofectAMINE Plus reagents (Invitrogen) in six-well plates. To normalize experiments for transfection efficiency, cells were cotransfected with a β-galactosidase reporter plasmid driven by cytomegalo virus promoter. The cells were harvested 24 h after transfection and extracted with reporter lysis buffer (Promega), and 20 μL of extract were used for the assay of luciferase activity as described (19). When indicated, heat-killed *Lm* was added to the culture for 6 to 12 h before harvest. The similar strategy was used for transfection of NF-κB-luciferase reporter plasmid to human gastric carcinoma cells.

**Reverse transcription-PCR.** Tumor cells were homogenized with Trizol reagent (Invitrogen), and total RNA was extracted according to the manufacturer's instructions. A reverse transcription-PCR (RT-PCR) procedure was used to determine relative quantities of mRNA (One-Step RT-PCR kit, Qiagen). Twenty-eight PCR cycles were used for all of the analyses, and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) was used as the internal control. The primers for all genes tested were described as follows: GAPDH, 5′-TGGGATGTTGCTCCACGAC-3′ (sense) and 5′-CAGTGGATGAGGGATGATGTCG-3′ (antisense); TLR2, 5′-GTCTTCTACCCTATTCCTCCT-3′ (sense) and 5′-GTTCTCATCTCTC-TATCTGT-3′ (antisense); TLR4, 5′-GAAACTCAGCAGCTCCGTG-3′ (sense) and 5′-GAAAGGCCTGTTGAGATG-3′ (antisense); interleukin-6 (IL-6), 5′-GAGAGGACCTCAGAGAATAC-3′ (sense) and 5′-GATCTCCAG-AAGCCAGGAGG-3′ (antisense); inducible nitric oxide synthase (iNOS), 5′-GAGATGGAGTTCGACTTCTGTG-3′ (sense) and 5′-TGTCATGTG-CCCTCGCTC-3′ (antisense).

**Assay for NO production and cytokine release.** NO production was measured using Greiss reagent (Sigma-Aldrich). Cytokine IL-6 in the supernatants of tumor cell culture was quantified by ELISA (R&D Systems). Bacteria Promote Tumor Progression

**Construction of H22 tumor cell lines expressing TLR2 and TLR4 siRNA.** TLR2 sense and antisense small interfering RNAs (siRNAs) were generated using Silencer siRNA construction kit according to the manufacturer's instruction (Ambion). After hybridization and purification, the different double-stranded TLR2 siRNAs and control siRNA were transiently transfected into H22 tumor cells using GeneSilencer siRNA transfection reagent (Gene Therapy Systems). The most efficient TLR2 siRNA sequence (gtcgcagagcaatac) and its control siRNA sequence (gtcgcagagcaatac) were verified by RT-PCR detection of TLR2 mRNA 24 h after transfection and inserted into RNAi-Ready pSIREN-RetroQ expressing vector with U6 promoter (BD Biosciences, Clontech). The TLR4 siRNA (gtcggcgtacgctt) and its control (gtcggcgtacgctt) siRNA-expressing vectors were constructed in the same way. The recombinant TLR2 and TLR4 siRNA-expressing plasmids and control plasmids were transfected into H22 tumor cell using FuGENE 6 transfection reagent (Roche) for stable expression after selection. Briefly, 48 h after transfection, puromycin was added to the medium to the final concentration of 15 μg/mL and the puromycin was replenished every 3 days. After 4-week selection, the clones were identified by RT-PCR.

**Statistical analysis.** Results were expressed as mean values ± SE deviation, and the difference was determined by the Student's *t*-test. A *P* value of <0.05 was considered significant.

**Results**

**Effects of *Lm* on tumor growth.** To analyze the interrelationship between *Lm* and tumor, we first examined the effects of *Lm*
vaccination on tumor growth. When mice were inoculated with H22 tumor cells after vaccination by i.v. injection with Lm and received second vaccination with a 20-fold higher i.v. dose of Lm 7 days later, the growth of tumor was significantly suppressed (Fig. 1A). Depletion of NK cells abrogated the antitumor effect of Lm vaccination (Fig. 1A), suggesting the importance of NK cells for this effect.

To explore the possibility of increasing the antitumor effect of Lm vaccination by Lm-specific cytotoxic T cells, we isolated Lm-specific T cells from Lm-vaccinated mice and determined their cytotoxicity toward Lm-infected tumor cells. The results of the cytotoxicity assay showed that splenocytes from Lm-vaccinated mice effectively killed Lm-infected H22 cells and macrophages but
Bacteria Promote Tumor Progression

The growth of tumor cells was accelerated by cultured in the presence or absence of Lm or H. pylori, respectively, and the proliferation of cells was quantified as described in Materials and Methods. *, P < 0.05, Student’s t test, significantly different from control. B and C, Lm survived in local tumor. Tumor cells (2 × 10^6) were inoculated s.c., and on day 15 (B) or day 3 (C) after tumor inoculation, 4 × 10^6 (high dose) or 4 × 10^5 (low dose) CFU of live Lm were injected i.v. On day 3 or day 10 after Lm injection, the bacteria in spleen and tumor tissue were quantified as described in Material and Methods. D, Lm promoted the growth of large tumor. Mice were inoculated with 2 × 10^5 H22 tumor cells, and 1 × 10^6 CFU of live Lm were injected directly into the tumor on days 3 and 15, respectively.

had minimal cytotoxicity to control H22 cells (Fig. 1B). To validate this in vitro result in vivo, we injected Lm into the tumor mass in Lm-vaccinated mice. However, the injection of Lm into the tumor promoted instead of inhibiting tumor growth (Fig. 1C).

The protumor effect of Lm is not due to cell-mediated immunosuppression. To explain the unexpected positive effect of Lm on tumor growth, we hypothesized that Lm injected into the tumor enhanced the immune escape through cell-mediated immunosuppressive effect. To test this, we investigated the effect of Lm in the presence or absence of Treg or MSC, the main immunosuppressive cell types in tumors (20–23). The injection of Lm promoted the growth of tumor (Fig. 2A), which, however, was not due to the effect of Lm on immunosuppressive cells. First, depletion of either Treg or MSC did not abrogate the effect of Lm on tumor growth (Fig. 2A). Second, 10 days after the injection of Lm into the tumor, the proportions of CD4+CD25+ Treg and Gr-1+CD11b+ MSC were unchanged in both tumor and spleen relative to those in control mice (Fig. 2B), indicating that Lm did not influence these immunoregulatory cells.

Bacteria interact directly with tumors in vitro. Based on the above data, we further hypothesized that Lm could directly promote the growth of tumor cells. To test this, H22 cells were cultured in the presence or absence of Lm. We found that the growth of tumor cells was accelerated by Lm (Fig. 3A), indicating that Lm could affect tumor cells by direct interaction. In agreement with these results, when gastric tumor cells from H. pylori−negative patients were cultured in the presence of live H. pylori isolated from H. pylori−positive gastric cancer patients, the growth of human gastric tumor cells was accelerated relative to controls (Fig. 3A). Same stimulating effect was observed by using heat-killed H. pylori (data not shown).

Survival of bacteria in tumors. A prerequisite for the direct effect of bacteria on tumor proliferation is the presence of bacteria within the tumor for a relatively long period. To verify this, the mice with either large tumors or impalpable tumors were injected i.v. with either high or low doses of Lm. On day 3 after the injection of Lm, viable bacteria were quantified in spleens of each group and also in the large tumors. On day 10 after the injection, viable Lm was found only in tumor tissues receiving Lm injection 15 days after tumor inoculation (Fig. 3B), but not in those receiving Lm injection 3 days after tumor inoculation (Fig. 3C) nor in the spleen of either group, indicating that Lm could only survive for a longer period in large tumors. In agreement with these observations, when Lm was injected directly into tumor inoculation sites of unvaccinated mice, Lm only promoted the growth of large tumors that were 7 × 7 mm at the time of Lm injection but not that of tumors that were impalpable at the time of Lm injection (Fig. 3D), suggesting that the continuous existence of Lm in tumor is needed for its tumor-promoting effect.

Bacteria increase the activation of mitogen-activated protein kinases and NF-κB in tumor cells. The increase in proliferation in the presence of bacteria suggests that the bacteria directly affect tumor cell signaling pathways. We therefore analyzed mitogen-activated protein kinases (MAPK) and NF-κB pathways commonly activated by pathogens. In the presence of Lm, the activation of MAPKs extracellular signal-regulated kinase (ERK) and c-Jun NH2-terminal kinase (JNK) in H22 cells was obviously increased (Fig. 4A). The activity of NF-κB in H22 cells was also
significantly increased in the presence of heat-killed Lm (Fig. 4B), evaluated with a NF-κB-luciferase reporter plasmid. The increased activity of NF-κB on stimulation of H22 cells by Lm was further confirmed by the increased expression of mRNA and protein for the downstream target genes iNOS and IL-6 (Fig. 4C). Comparable results were obtained following incubation of heat-killed Lm with B16 melanoma cells (data not shown). To generalize these results to human tumors, we tested the NF-κB activity of gastric tumor cells after H. pylori stimulation. Tumor cells were isolated from H. pylori–negative gastric cancer patients, transfected with a NF-κB-luciferase reporter plasmid, and cultured in the presence of H. pylori isolated from H. pylori–positive patients. NF-κB activity was induced in the tumor cells by incubation with H. pylori, and the NF-κB–regulated genes iNOS and IL-6 were also strongly induced (Fig. 4D).

**Lm triggers the signal transduction in tumor cells through TLR2.** Our previous study indicated that tumor cells express a variety of TLRs and that NF-κB and MAPKs are the signal transducers in TLR signaling pathway. To test the hypothesis that TLR stimulation of tumor cells induces the cytokine secretion and proliferation we observed on incubation with bacteria, we constructed TLR2 and TLR4 knockdown H22 tumor cell lines (Fig. 5A). The TLR2 knockdown tumor cells, but not TLR4 knockdown tumor cells, largely failed to respond to Lm, judged by the activation of NF-κB and production of NO and IL-6 (Fig. 5B), indicating that TLR2, rather than TLR4, was important for Lm signaling.

To further elucidate the role of TLR2 in the tumor-promoting effect of Lm, we investigated the influence of Lm on proliferation and tumor growth in the presence or absence of TLR2 signaling. The stimulation with Lm significantly increased proliferation of both WT and TLR4 knockdown H22 tumor cells relative to that of cells without Lm stimulation but not that of TLR2 knockdown H22 cells (Fig. 5C). Finally, Lm was directly injected into large tumor formed by TLR2 knockdown H22 cells. In the absence of TLR2 signaling, Lm had no effect on tumor growth compared with that of the control group (Fig. 5D). Taken together, these data indicate that TLR2, but not TLR4, is required for Lm–triggered signal transduction of H22 tumor cells to promote tumor growth.

**Discussion**

It has been suggested that chronic bacterial infection may play a role in tumorigenesis and that the underlying mechanisms are connected with the infection-mediated inflammation (1–3). In this study, we provide new insight into the relationship between bacteria and tumorigenesis. The direct interaction of bacteria with...
Toll-like receptor (TLR2) of tumor cells promoted tumor growth by the activation of NF-κB and MAPKs, leading to the acceleration of tumor cell proliferation and secretion of IL-6 and NO.

NF-κB functions as a tumor promoter in inflammation-associated cancer (24, 25). The activation of NF-κB is a critical mechanism leading to protection of tumor cells from apoptotic stress (6). NF-κB also induces cell proliferation and augments angiogenesis by enhancing the expression of vascular endothelial growth factor (26). Although it is known that TLR-mediated signal transduction leads to the activation of NF-κB (27, 28), the mechanism whereby NF-κB is chronically activated in tumors still remains to be elucidated. We report that long-term activation of NF-κB in tumors may be due to persistence of bacteria within the tumor. Significantly, knockdown of TLR2, but not TLR4, inhibited Lm-induced IL-6 and NO secretion as well as enhanced tumor proliferation. The promotion of tumor growth by bacteria has been reported to require the induction of host systemic or local immune suppression. Recombinant Lm and other bacteria have been reported (3, 12) to induce the generation of Treg in tumor-bearing hosts. However, in our tumor model, Lm had no effect on numbers of either Treg or MSCs within 10 days. We suggest that immunosuppression can be initiated rapidly by engagement of tumor TLRs, resulting in a cascade leading to tumor evasion from immune surveillance (14). NO and IL-6 produced by tumor cells, induced by lipopolysaccharide activation of the TLR4 signaling pathway, inhibits T-cell proliferation and NK cell activity (14). We found in this study that the production of NO and IL-6 was induced by Lm through TLR2 pathway, indicating that Lm stimulated the production of immunosuppressive molecules by tumor cells.

Genetically modified nonpathogenic bacteria have been used to deliver immune-activating or tumoricidal molecules for cancer therapy (29–31). Recent reports indicated that bacteria, such as Salmonella (32) and Lm (11, 33), can be used for tumor therapy, which requires high doses of bacteria, small initial tumor burden, and prevaccination with either recombinant bacterial vaccine or bacteria-loaded dendritic cells. However, in large tumors, we show that bacteria may persist after systemic bacterial clearance due to immunosuppressive cells and cytokines that may inhibit local immune cell-mediated bacterial killing. This immunosuppression may also partially explain why Lm-activated T cells cannot efficiently eliminate Lm-infected tumor cells in vivo.

In summary, our findings revealed a direct interaction between bacteria and tumor cells using a Lm-infected tumor model. Significantly, this phenomenon was also observed in clinical samples of H. pylori–associated gastric carcinoma. The infection-induced inflammation due to the activation of tumor cell NF-κB is likely to be an important factor favoring tumor progression. However, attention should also be paid to the effects of the pathogens on the tumors because the signaling induced by the interaction between bacteria and tumor cell TLR results in the continuous activation of NF-κB and MAPKs in tumor cells and thus drives proliferation directly.

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