Autoimmune Gastritis Mediated by CD4+ T Cells Promotes the Development of Gastric Cancer

Thanh-Long M. Nguyen1, Shradha S. Khurana3, Clifford J. Bellone1, Benjamin J. Capoccia3, John E. Sagartz2, Russell A. Kesman Jr1, Jason C. Mills3, and Richard J. DiPaolo1

Abstract

Chronic inflammation is a major risk factor for cancer, including gastric cancers and other gastrointestinal cancers. For example, chronic inflammation caused by autoimmune gastritis (AIG) is associated with an increased risk of gastric polyps, gastric carcinoid tumors, and possibly adenocarcinomas. In this study, we characterized the progression of gastric cancer in a novel mouse model of AIG. In this model, disease was caused by CD4+ T cells expressing a transgenic T-cell receptor specific for a peptide from the H+ /K+ ATPase proton pump, a protein expressed by parietal cells in the stomach. AIG caused epithelial cell aberrations that mimicked most of those seen in progression of human gastric cancers, including chronic gastritis followed by oxyntic atrophy, mucous neck cell hyperplasia, spasmodic polypeptide-expressing metaplasia, dysplasia, and ultimately gastric intraepithelial neoplasias. Our work provides the first direct evidence that AIG supports the development of gastric neoplasia and provides a useful model to study how inflammation drives gastric cancer. Cancer Res; 73(7); 2117–26. ©2013 AACR.

Introduction

Autoimmune gastritis (AIG) is one of the most common autoimmune conditions in humans and is caused when the adaptive immune system (T and B cells) targets self-antigens expressed by parietal cells and chief cells in the gastric mucosa. AIG may persist in an asymptomatic form for many years. A subset of individuals will eventually develop pernicious anemia (PA). Pernicious anemia is the major cause of vitamin B12 deficiency. AIG and pernicious anemia have respective prevalence of 2% and 0.15% to 1% in the general population (1, 2), which is increased 3- to 5-fold in individuals with other, concomitant autoimmune diseases, such as type 1 diabetes (3, 4) and autoimmune thyroid disease (5, 6). Gastric carcinoid tumors, evolving from enterochromaffine-like (ECL) cell hyper/dysplasia induced by hypergastrinemia, develop in 4% to 9% of patients with AIG/PA (7–9). Gastric carcinoid tumors are relatively benign lesions, metastasizing in less than 10% of cases (10). Several studies have examined whether individuals with AIG/PA also have a higher risk of developing gastric adenocarcinomas, which is the second leading cause of cancer related deaths in the world. Two recent studies, one with 4.5 million retired male veterans in the United States and the other included 9 million individuals from Sweden, reported that individuals with pernicious anemia had an increased risk of developing not only gastrointestinal carcinoids but also stomach adenocarcinomas, small intestinal adenocarcinomas, squamous cell carcinomas (SCC), and esophageal SCCs (11, 12).

Gastric cancer is the fourth most common cancer and the second most deadly malignant neoplasm in the world. A model, referred to as the Correa pathway, describes the development of gastric adenocarcinomas in humans from a histologic perspective (13). This model details the progression of gastric cancer through a series of pathologic steps the epithelium undergoes starting with chronic inflammation (gastritis), followed by atrophy (especially loss of parietal cells), metaplasia, dysplasia, and eventually neoplasia. A better understanding of how inflammation induces gastric epithelial cell changes could provide potential therapeutic strategies for diagnosing and preventing gastric cancer (14). To gain a better understanding of the progression of gastric cancer from a cellular and molecular perspective, numerous groups have developed animal models, mouse models in particular, to study gastric carcinogenesis. Such strategies have included chronic infection with Helicobacter (15), chemical depletion of parietal cells (16, 17), and several different lines of genetically modified mice. While these models have increased our understanding of the roles of infection, parietal cell loss, and genes involved in regulating epithelial cell biology, none have directly examined the role of chronic inflammation as the primary inducer of epithelial cell change, which would be useful for understanding the roles of cytokines and immune cells in promoting gastric cancer and for addressing the potential link between AIG and gastric cancer.

Published OnlineFirst February 1, 2013; DOI: 10.1158/0008-5472.CAN-12-3957

©2013 American Association for Cancer Research.

www.aacrjournals.org
We investigated the potential link between AIG and gastric cancer using a T-cell receptor (TCR) transgenic mouse model of AIG (18). These transgenic CD4+ T cells recognizes a peptide from the parietal cell specific antigen H+/K+-ATPase, which is also the major autoantigen targeted by the immune system in humans with AIG/PA (19). All mice developed chronic gastritis that resulted from large numbers of CD4+ T cells that infiltrated the gastric mucosa and produced large amounts of IFN-γ and smaller amounts of interleukin (IL)-17. Mice developed severe oxyntic atrophy and metaplasia by 2 to 4 months of age. At this stage of disease, mice also developed several molecular features associated with the progression of gastric cancer in humans, including spasmolytic polypeptide expressing metaplasia (SPEM), increased levels of mRNA for gastric cancer biomarkers (HE4, OLFM4, TFF2), and increased levels of phosphorylated STAT3 compared with nontransgenic control mice. Finally, by 12 months of age, all mice with AIG developed high-grade dysplasia consistent with gastric intraepithelial neoplasia (GIN). In summary, we report a new mouse model showing that inflammation associated with AIG induces many of the pathologic and molecular features of gastric carcinogenesis, including the development of severe dysplasia/GIN. These studies support a link between AIG and gastric cancer and highlight the importance of localized inflammation in the development of stomach cancer. This new, immune system-induced model of gastric cancer will be useful for studying important host factors that influence inflammation-induced adenocarcinomas.

Materials and Methods

Mice

TxA23 TCR transgenic mice have been previously described and have been bred more than 15 generations onto the BALB/c background (18). The BALB/c control mice described in these experiments are TCR transgene-negative littermates that were co-housed with the TxA23 TCR transgenic mice. All mice were maintained under specific pathogen-free conditions and cared for in our animal facility in accordance with institutional guidelines. Our colony tested negative by PCR for the following: Helicobacter sp., Helicobacter bilis, Helicobacter hepaticus, Helicobacter rodentium, Helicobacter sp., Helicobacter trogontum, and Helicobacter typhi.

Histopathology

Stomachs were removed from mice, rinsed in saline, immersed in 10% neutral-buffered formalin (Thermo Scientific), paraffin-embedded, sectioned, and stained with hematoxylin and eosin. Pathology scores were assigned using methods modified from Rogers and colleagues (20). Slides were blinded and sections from individual mice were assigned scores between 0 (absent) and 4 (severe) to indicate the severity of inflammation, oxyntic atrophy, mucinous hyperplasia/meta-plasia, and dysplasia. Scores were validated by an independent second pathologist blinded to experimental conditions.

Immunofluorescence

Stomachs were fixed for 20 minutes with methacarn (60% methanol, 30% chloroform and 10% glacial acetic acid; all from Fisher), washed with 70% ethanol, embedded in paraffin, and sectioned into 0.5-μm thick sections. Slides were deparaffinized, rehydrated, stained, and imaged using methods modified from Ramsey and colleagues (21). The primary antibodies used for immunostaining were rabbit anti-human gastric intrinsic factor (gifts of Dr. David Alpers, Washington University, St. Louis, MO), rabbit anti-Ki67 (Abcam), and mouse anti-Ecadherin (BD Biosciences). Secondary antibodies and GSII lectin (Molecular Probes) labeling were as described (21).

A gastric unit is defined as an invagination of the gastric mucosa that is lined by a single layer of columnar epithelium. Each gastric unit is lined by foveolar cells at the luminal end and zymogenic cells at the base. Ki67 staining was quantified by counting each Ki67+ nucleus per gastric unit for more than 50 units per mouse and classified into <10, 10–20, and >20 positive nuclei per unit. Percentages were calculated by dividing the number of gastric units in each category by total number of gastric units analyzed in that mouse stomach sample.

Immunohistochemistry

Tissue was deparaffinized and rehydrated. Endogenous peroxidase was blocked using a 0.3% H2O2 in methanol for 15 minutes. Antigen retrieval was done in a pressure cooker with Diva (Biocare: DV2004MX). Avidin/biotin kit (Biocare) was used to block endogenous biotin. The antibody pStat3 (D3A7) from Cell Signaling was diluted in Davinci (Biocare) and incubated over night at 4°C. The secondary antibody, biotinylated goat anti-rabbit, and streptavidin-HRP from Jackson Labs were each applied for 1 hour at room temperature. Visualization was done with Biocare's Betaziod DAB and slides were counterstained in hematoxylin.

Immunoblot

A section from the stomach was homogenized with an electric pestle tissue homogenizer. Cells were then lysed in 0.5 mL of lysis buffer [20 mmol/L Tris-HCl pH 7.5, 150 mmol/L NaCl, 1 mmol/L Na2EDTA, 1 mmol/L EGTA, 1% Triton, 2.5 mmol/L sodium pyrophosphate, 1 mmol/L β-glycerophosphat, 1 mmol/L Na2VO4, 1 μg/mL leupeptin (Cell Signaling) and a protease inhibitor cocktail (Sigma)]. Lysates were vortexed for 1 minute and sonicated for 15 seconds followed by centrifugation for 10 minutes at 4°C. Lysates were ran on a NuPAGE 4% to 12% Bis-Tris gradient gel (Novex) and transferred to a nitrocellulose membrane. Membrane was blocked for 1 hour with 5% nonfat dairy milk. Primary antibodies (all from Cell Signaling) were stained for 1 hour (rabbit mAB-β-actin- and rabbit mAB-STAT3) or overnight (rabbit mAB phospho-STAT3) in 5% bovine serum albumin (BSA) in 4°C. Horseradish peroxidase-linked secondary antibody (anti-rabbit IgG) was stained for 1 hour at room temperature in 5% nonfat dairy milk. Protein was detected by chemiluminescence using LumiGLO (Cell Signaling) on CL-XPosure X-Ray film (Fisher).

Flow cytometry

Cell surface staining was conducted according to standard procedures using monoclonal antibodies against CD4,
CD19, CD11b, and Ly6G. Intracellular cytokine staining was conducted using monoclonal antibodies against IFN-γ and IL-17A. All antibodies were purchased from BD Pharmin- gen. All flow cytometry was conducted on a BD LSRII or BD FACS Calibur and analyzed using FlowJo (TreeStar). For intracellular cytokine staining, cells were stimulated with PMA (Calbiochem) and Ionomycin (Calbiochem) for 4 hours at 37°C. Golgi-stop (BD Biosciences) was added after 1 hour. Cells were then washed, fixed in 4% formyl saline, washed, and permeabilized (0.5% BSA, 0.1% Triton, and 2 mmol/L EDTA in PBS) for 1 hour at room temperature. After washing, cells were incubated overnight with the anti-cytokine antibodies, washed, and analyzed by flow cytometry.

Isolation of cells from the gastric lymph nodes and gastric mucosa

The method for isolating cells from the stomach tissue has been described previously (22, 23). Briefly, the gastric lymph nodes (gLN) were removed from the stomachs, homogenized, and passed through a 40-μm nylon filter. Stomachs were opened with an incision from the antrum to the fundus and rinsed in PBS to remove food. Cells were flushed from the gastric mucosa using a syringe with a 25-gauge needle. PBS containing 5% fetal calf serum and penicillin/streptomycin (Sigma) was repeatedly injected within the mucosa causing the tissue to swell and rupture. Single-cell suspensions were collected, gently vortexed, and passed through a 40-μm nylon filter. Cells were counted, stained with antibodies, and analyzed by flow cytometry. To detect secreted cytokines, 1 × 10^6 cells were culture in vitro in 24-well plates containing 2 mL of supplemented RPMI. Supernatants from cell cultures were collected after 48 hours, and cytokines and chemokines were measured using Milliplex (Millipore).

Quantitative real-time PCR

Total RNA was prepared using the RNeasy Mini Kit System (Qiagen). The quantity and quality of RNA were determined using a NanoDrop 2000 spectrophotometer (Thermo Scientific), and 0.5 μg of the RNA was used to generate a first-strand cDNA copy according to the manufacturer's instruction (High Capacity cDNA Reverse Transcription Kit, Applied Biosystems). Quantitative PCR was carried out using TaqMan Gene Expression Assays systems (Applied Biosystems). Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) served as an internal reference standard. PCR was run on the 7500 Real-Time PCR System (Applied Biosystems).

Statistical analysis

Data are expressed as means of individual determinations ± SE. Statistical analysis was conducted using the Mann–Whitney test (*, P < 0.05; **, P < 0.01; ***, P < 0.001) using GraphPad Prism 5.
Results

**Inflammation in TxA23 mice is characterized by CD4\(^+\) T cells secreting IFN-\(\gamma\) and IL-17**

Our first goal was to characterize the cell types and cytokines in TxA23 mice. Cells were isolated from the gastric mucosa and gastric lymph nodes of 2-month-old mice and analyzed by flow cytometry. The majority (>85%) of the hematopoietic-derived cells isolated were either CD4\(^+\) T cells or CD19\(^+\) B cells (Fig. 1A). As expected, the majority of the CD4\(^+\) T cells that infiltrated the stomach expressed the transgenic TCR (TCRV\(_{a2}/TCRV_{b2}\)) specific for the H\(^+\)/K\(^+\) ATPase peptide (Fig. 1B). Macrophages (CD11b\(^+\)Ly6G\(^-\)) and neutrophils (CD11b\(^+\)Ly6G\(^+\)) and a subset of dendritic cells (CD11b\(^-\)CD11c\(^+\), data not shown) comprised the rest of the cells found in the gastric mucosa (Fig. 1C). Next, cells were restimulated and cytokine production by CD4\(^+\) T cells was determined by intracellular cytokine staining. The majority of cytokine-producing CD4\(^+\) T cells isolated from the stomachs and gastric lymph nodes produced IFN-\(\gamma\) and fewer produced IL-2 and IL-17. IL-4 secretion by CD4\(^+\) T cells was not detected (Fig. 1D). Finally, total cells isolated from the gastric lymph node were cultured immediately after isolation. The amounts of several cytokines secreted into the supernatants were determined after 48 hours. The most abundant cytokines secreted by cells were IFN-\(\gamma\) and IL-17 (Fig. 1E). Lower levels of IL-6, IL-2, IL-10, and IL-4 were also detected. Thus, the inflammatory infiltrate within the gastric mucosa consists primarily of a mixture of T-helper cells (T\(_{h1}\) (IFN-\(\gamma\)) and T\(_{h17}\) (IL-17\(^+\)) CD4\(^+\) T and B cells. This type of inflammation is consistent with the type of inflammation described in humans infected with *H. Pylori* and with autoimmune gastritis (24, 25).
TxA23 progress through a series of pathological changes associated with the development of gastric cancer

In humans, the progression of intestinal-type gastric cancer is thought to evolve through a series of discrete steps known as the Correa pathway (13). The first step in this pathway is inflammation (gastritis) and then loss of parietal cells (oxyntic atrophy) and the development of mucinous metaplasia, followed by dysplasia and finally
cancer. We examined the pathologic features of gastric disease in TxA23 mice. At 2 months of age, TxA23 mice had moderate degrees of inflammation, oxyntic atrophy, and mucosal hyperplasia/metaplasia but little or no evidence of dysplasia (Fig. 2A). By 4 months of age, inflammation, oxyntic atrophy, and mucosal hyperplasia/metaplasia were significantly more severe than 2-month-old mice (Fig. 2A). Lesions in the stomachs of 4-month-old TxA23 mice comprised large areas in which parietal cells were either reduced in number or absent from the gastric units, and the remaining mucosa was dominated by large, hyperplastic mucous-containing cells that expanded to the bases of gastric units (Fig. 2B and C). Four of the 19 mice had developed mild focal dysplasia (Fig. 2D). For comparison, Fig. 2E is representative of the normal pathology observed in 11 individual control mice, which are transgene-negative BALB/c mice that were cohoused with TxA23 littermates. Disease severity was similar in male and female mice at all ages. These data show that chronic inflammation resulting from autoimmune gastritis induced the development of preneoplastic lesions in the gastric mucosa of TxA23 mice with many pathologic features in common with the Correa pathway.

**Increased epithelial cell proliferation, phosphorylated STAT3, IL-6, and expression of gastric cancer–associated biomarkers in TxA23 mice**

Next, we used immunofluorescence to compare the extent of gastric epithelial cell proliferation in 2- and 4-month-old TxA23 mice compared with BALB/c control mice (Fig. 3A–C). In wild-type BALB/c mice, the number of proliferating (marked by Ki67+ immunoreactivity) epithelial cells (marked by E-cadherin+) per individual gastric unit was always less than 10. However, in TxA23 mice, almost 70% of 2-month-old gastric units had 10 or more proliferating cells, and by 4 months, more than 75% had more than 10 with about a third of those having 20 or more (Fig. 3D).

Increased levels of the active (phosphorylated) pSTAT3 is involved in cellular transformation in numerous cancers of epithelial origin, including gastric cancer (26). A recent study suggested that pSTAT3 is a significant prognostic factor in gastric cancer in humans (27). To determine whether the level of pSTAT3 was increased in the stomachs of TxA23 mice, we conducted Western blots on gastric tissue lysates from age-matched TxA23 and healthy BALB/c control mice. Compared with BALB/c mice, TxA23 mice expressed slightly higher levels of total STAT3 and a much higher level of pSTAT3 (Fig. 4A). Immunohistochemical analysis revealed a large number of pSTAT3-positive epithelial cells present in the gastric mucosa of TxA23 mice and nearly undetectable levels in gastric tissue from BALB/c controls (Fig. 4B), in agreement with the results observed by Western blotting.

Several members of the IL-6 cytokine family, including IL-6 and IL-11, activate STAT3 (28). IL-6 and IL-11 have important roles in maintaining gastric homeostasis by regulating mucosal proliferation, inflammation, angiogenesis, and apoptosis (29, 30). We conducted quantitative real-time PCR analysis using mRNA isolated from gastric tissue from 2-month-old TxA23 and BALB/c mice to measure the relative levels of IL-6 and IL-11. The levels of IL-11 mRNA were equivalent between the 2 genotypes; however, the levels of IL-6 mRNA were approximately 40-fold higher in TxA23 mice than in BALB/c mice (Fig. 4C).

A number of genes have been described as biomarkers for precursor lesions such as SPEM that are predisposing for gastric cancer. Some of these genes include human epididymis 4 (HE4; ref. 16), Trefoil factor 2 (TFF2), and Olfactomedin 4 (OLFM4; ref. 31). HE4 is absent in normal stomach and expressed in humans and mice with SPEM (16). Increased levels of OLFM4, also known as GW112, have been observed in gastric cancers, including 58% of stage III/IV gastric cancers (31). TFF2 is also known as spasmolytic polypeptide,
and, by definition, increases when SPEM is present. We carried out quantitative real-time PCR analysis using mRNA isolated from sections taken from the body of the stomachs of TxA23 mice. All of the TxA23 mice expressed higher levels of *HE4* and *OLFM4*, and a majority, 5 of 7 mice, expressed higher levels of *TFF2* than age-matched BALB/c control mice (Fig. 4D). Together, these data show that disease in TxA23 mice shares many of the molecular features of gastric cancer that have been reported in humans, including increased epithelial cell proliferation, increased levels of pSTAT3 protein, and higher levels of *IL-6, HE4, OLFM4*, and *TFF2* mRNA.

**SPEM is present in the gastric mucosa of TxA23 mice**

Intestinal-type gastric cancer predominantly develops in the setting of oxyntic atrophy and mucous cell metaplasia (13). Spasmolytic polypeptide–expressing metaplasia (SPEM) is a metaplasia in the gastric fundus resembling deep antral gland cells, and recent studies have indicated that SPEM may be directly linked to gastric neoplasia (25, 32). We used immunohistochemistry to determine whether 4-month-old TxA23 mice developed SPEM. A representative section from a TxA23 mouse is shown in Fig. 5A. In gastric units in which parietal cells have not yet been destroyed, chief cells are found at the base of the unit and are identified by staining with antibodies to gastric intrinsic factor (GIF). Of note, the antrum/pyloris of TxA23 mice were indistinguishable from BALB/c control mice. In the corpus region, neck cells are found above and identified by lectin GSII staining (Fig. 5B). However, we also observed multiple gastric units in which the majority or all of the parietal cells had been lost (Fig. 5B and C). In these parietal cell–depleted units, there was an expansion of GSII-positive cells (mucous neck cell hyperplasia) and an emergence of cells expressing both neck cell–specific and chief cell-specific markers (GIF) in the base of the units, whereas in regions with parietal cell preservation, the normal basal marker expression pattern was maintained (Fig. 5D). Thus, GSII-positive GIF-positive cells in the base of gastric units that lack parietal cells also stained positive for TFF2 (data not shown), showing that TxA23 mice developed regions of SPEM by 4 months of age.

**TxA23 mice develop GIN**

In the next set of experiments, we allowed a cohort of TxA23 mice to age and conducted histopathologic evaluations to determine whether disease in TxA23 mice progressed beyond SPEM to dysplasia. Sections from stomachs of 4- and 12-month-old mice were examined by a pathologist using a murine gastric histopathology scoring paradigm described previously (ref. 20; Fig. 6A). The analysis of mice at 4 months of age revealed that 15 of 19 had dysplasia scores of 0 and 4 of 19 mice had dysplasia scores of 1, indicating focal irregularly shaped gastric glands, including elongated, slit, trident, and back-to-back forms (Fig. 6B). By 12 months of age, disease progressed to the point at which 7 of 8 mice developed severe dysplasia, indicated by scores of 3.5. In this scoring system a score of 3 is used to indicate severe loss of gland organization and columnar orientation, marked cell atypia, visible mitoses, GIN, and 0.5 is added for carcinoma in situ or invasion without frank malignancy. We observed both focal and widespread dysplasia and most cases involved pseudo invasion into the submucosa and/or serosa (Fig. 6C–E). We also observed the formation of irregular...
glandular forms on the adventitial surface of the stomach, some of which contained papillary projections of atypical epithelium (Fig. 6F). These data show that precancerous lesions observed in 4-month-old TxA23 mice ultimately progressed to neoplastic disease.

Discussion

Although chronic atrophic gastritis is believed to be important in initiating gastric carcinogenesis, the precise role(s) of inflammation in the complex changes in gastric epithelial cells during the progression of gastric cancer are not understood. Furthermore, the relationship between AIG/PA and gastric cancer has been controversial and requires further investigation. In this study, we describe a new mouse model showing that autoimmune gastritis induces precancerous lesions similar to those that precede gastric cancer in humans. Mice with chronic inflammation caused by H⁺/K⁺ ATPase-specific CD4⁺T cells developed severe oxyntic atrophy coupled with metaplasia, including SPEM by 4 months of age. Similar to H. pylori infection and AIG in humans, inflammation in TxA23 mice contained CD4⁺ T cells of the T₃H1 (IFN-γ⁺) and T₁H17 (IL-17⁺) phenotype (33, 34). Consistent with the Correa pathway that describes the progression of gastric cancer in humans, TxA23 mice progressed through a series of stages that included inflammation, atrophic gastritis, mucous neck cell hyperplasia, SPEM, which over time progressed to dysplasia, and neoplasia. These data indicate that the TxA23 model system is unique in that it allows for the study of the development and regulation of gastric carcinogenesis in a setting where chronic inflammation, in the absence of infection, toxins, and drugs, is the primary upstream instigator. Our findings of carcinogenesis in our mouse model are consistent with reports that humans with AIG/PA are 3 to 6 times more likely to develop gastric adenocarcinoma and other cancers (35, 36). It has been reported that a subset of individuals contain T cells and antibodies specific for H⁺/K⁺ATPase after they are infected with H. pylori (37–40). It is possible that individuals that develop autoimmune responses during H. pylori infection may remain at risk for gastric cancer even if they are treated for H. pylori infection. Studies have shown that the eradication of H. pylori reduces risk for subsequent gastric cancer by about 25% (40–42). Strategies to reduce inflammation in addition to eradicating H. pylori may further reduce the risk of gastric cancer.

With the two recent studies reporting that individuals with pernicious anemia developed gastrointestinal cancers at a higher-than-expected rate, animal models that mimic AIG are likely to be useful for understanding the link between AIG and GI cancers. There is no doubt that infection with H. pylori is an important, prerequisite risk factor for gastric cancer; however, the vast majority of infected patients do not develop cancer. Therefore, it may be the types of chronic inflammation in the gastric mucosa that is triggered by H. pylori that are downstream adjuvants or causes of actual cancer. The TxA23 mouse
model described here mimics the human disease and shows the progression of AIG to the development of SPEM and eventually severe to dysplasia. Other genetically engineered mouse models have been useful for studying factors that influence the development of gastric cancer independently of Helicobacter infection. For example, mice expressing gastrin under the insulin promoter (43), mice deficient in: TFF1 (44), Smad4 (45), and Hipt1 (46), and mice expressing a mutated form of the IL-6 family coreceptor gp130 (47) all develop forms of gastric metaplasia and some cases dysplasia. Our model specifically focuses on the immune response to $H^+/K^+$ ATPase and its role in promoting SPEM with progression to severe dysplasia. By inducing severe dysplasia in the absence of infection, this model will allow for a direct examination of the mechanisms whereby inflammation influences gastric epithelial cell biology. For example, when examining disease in cytokine knockout mice, using our model, we do not have to be concerned with the potential indirect effects of the importance of the cytokine in modulating Helicobacter infection itself. Our model will be also be useful for evaluating the importance of immune cells, such as regulatory T cells, and how they influence changes in gastric epithelial cells that are associated with the progression of gastric cancer. Finally, future studies using this model will address how various host factors, especially immune-related genes, influence the risk of developing gastric cancer.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

References

Autoimmune Gastritis Mediated by CD4+ T Cells Promotes the Development of Gastric Cancer


Cancer Res 2013;73:2117-2126. Published OnlineFirst February 1, 2013.

Updated version Access the most recent version of this article at:
doi:10.1158/0008-5472.CAN-12-3957

Cited articles This article cites 47 articles, 16 of which you can access for free at:
http://cancerres.aacrjournals.org/content/73/7/2117.full.html#ref-list-1

E-mail alerts Sign up to receive free email-alerts related to this article or journal.
Reprints and Subscriptions To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.
Permissions To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.