Claudin-4, Mitogen-Activated Protein Kinase Kinase 4, and Stratifin Are Markers of Gastric Adenocarcinoma Precursor Lesions

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Abstract

Approximately 23,000 new gastric cancer cases and 12,000 associated deaths occur annually in the United States. Intestinal metaplasia and gastric epithelial dysplasia are precursor lesions to gastric adenocarcinoma, but are not readily detectable clinically, radiographically, or endoscopically. A noninvasive method of precursor detection would require the ability to distinguish precursor lesions from adjacent normal mucosa. In search of such markers, tissue microarrays were prepared for 133 patients of resected gastric adenocarcinoma. Tissue microarrays contained primary cancer, normal stomach, intestinal metaplasia, and gastric epithelial dysplasia and were probed with antibodies against nine potential markers that were either identified in a database of genes overexpressed in gastric adenocarcinoma or were already of interest to our laboratory: claudin-4, mitogen-activated protein kinase kinase 4 (MKK4), 14-3-3σ (stratifin), S100A4, mesothelin, fascin, topoisomerase IIα, HER-2/neu, and epithelial growth factor receptor. Three markers discriminated gastric adenocarcinoma precursor lesions from normal gastric mucosa. Claudin-4 expression was present in 36 intestinal metaplasia lesions (100%) and 14 gastric epithelial dysplasia lesions (100%), but in only 16 normal stomach samples (15%). MKK4 expression was present in 24 intestinal metaplasia lesions (89%) and 12 gastric epithelial dysplasia lesions (100%), but in only 6 normal stomach samples (8%). Stratifin expression was present in 29 intestinal metaplasia lesions (97%) and 8 gastric epithelial dysplasia lesions (100%), but in only 2 normal stomach samples (3%). Sensitivity and specificity for detection of the precursor lesion intestinal metaplasia were 100% and 85%, respectively, for claudin-4; 89% and 92%, respectively, for MKK4; and 97% and 97%, respectively, for stratifin. In primary cancers, 123 of 125 (98.4%) were positive for claudin-4, 116 of 126 (94%) for MKK4, and 111 of 120 (92%) for stratifin. In conclusion, claudin-4, MKK4, and stratifin immunolabeling detects precursor lesions of gastric adenocarcinoma that are otherwise clinically, radiographically, and endoscopically inapparent. These findings may prove useful in the diagnosis and therapeutic targeting of gastric adenocarcinoma precursor lesions. (Cancer Epidemiol Biomarkers Prev 2006;15(2):281–7)

Introduction

There are an estimated 22,710 new cases per year of gastric cancer in the United States, and ~11,780 of those patients will die of their disease (1). Gastric adenocarcinoma remains the second leading cause of cancer death worldwide, accounting for ~10% of all newly diagnosed cancers. Intestinal metaplasia is an asymptomatic, radiologically and endoscopically undetectable lesion considered to be premalignant. In 1955, Morson andstra 

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Materials and Methods

Tissue Microarrays. After approval from Johns Hopkins University Institutional Review Board, paraffin-embedded material from patients undergoing surgical resection at the Johns Hopkins Hospital was used for this study. Seven tissue microarrays, representing 133 patients, were constructed containing primary, metastatic cancer, and nonneoplastic stomach. Tissue microarrays were constructed using a manual Tissue Puncher/Arrayer (Beecher Instruments, Silver Spring, MD) as previously described (18). To avoid geographic or spatial patterning artifacts, the samples were not grouped by histology but were arranged in a semirandom pattern. For each selected lesion, a 1.4-mm core was punched from the donor block and a total of 99 cores was arrayed per block. Several serial sections were cut from all tissue microarrays, one of which was stained with H&E as a reference. Because serial sectioning of the tissue microarrays results in less than perfect application of every one of the 99 samples (1.4 mm), most arrays actually have fewer than 99 samples. Consequently, the number of samples available for immunolabeling may differ from antibody to antibody.

Immunohistochemistry. Claudin-4, MKK4, and stratifin expression was assessed by immunohistochemistry in 125, 124, and 120 gastric adenocarcinoma patient specimens, respectively. Immunohistochemistry was done on 5 μm paraffin sections of gastric tissue microarrays. Immunohistochemical analysis was done using the TECHMATE 1000 system (Ventana, Tucson, AZ). Monoclonal mouse antibodies recognizing claudin-4 (Zymed Laboratory, Inc., South San Francisco, CA), MKK4 (Novocastra, Newcastle upon Tyne, United Kingdom), or stratifin (NeoVision, Fremont, CA) were used at dilutions of 1:500, 1:40, and 1:100, respectively. Secondary antibody application and color development were done using the CHEM MATE 3Ab-Biotin (Biotinylated Link) and Detection Kit Peroxidase/DAB (Ventana Medical Systems, Cambridgeshire, United Kingdom) according to the instructions of the manufacturer (11). Each immunohistochemical sample was evaluated by two or three individuals (E. Montgomery, S.C. Cunningham, and C.A. Iacobuzio-Donahue), with agreement in all cases, using the following criteria: For claudin-4, 0 = absence of membrane staining; +1 = some membrane staining evident; 2+ = strong membrane staining; 3+ = very strong, complete membrane staining (Fig. 1); for MKK4, 0 = absence of cytoplasmic staining, 1+ = moderate cytoplasmic staining; 2+ = strong cytoplasmic staining (Fig. 2); and for stratifin, 0 = absence of staining; 1 = moderate cytoplasmic or perinuclear staining; and 2 = strong cytoplasmic or perinuclear staining (Fig. 3).

Expression of S100A4 (DAKO, Carpinteria, CA; dilution 1:500), mesothelin (clone 5B2, Novocastra; dilution 1:20), fascin (clone 55K-2, DAKO; dilution 1:100), topoisomerase II (Novocastra; dilution 1:100), HER-2/neu (DAKO; prediluted), and epithelial growth factor receptor (Ventana Medical Systems; dilution 1:50) were evaluated in the same tissue microarrays.

The possibility of nonspecific antibody interactions is different for each of these three antibodies. We have confirmed specificity of the anti-MKK4 antibody by calibrating the immunohistochemistry assay to known actual genetic status of the samples (19). Claudin-4 antibody specificity is shown by the internal controls on the tissue microarrays that contain the well-described intensely labeled positive-control colonic epithelium and the nonlabeled negative-control gastric epithelium (20). Stratifin, a substantially less well-characterized molecule, showed the immunohistochemical pattern previously reported (21).

Data Analysis. The proportion of positive samples was calculated in primary cancer, metastatic cancer, intestinal metaplasia, and normal gastric samples. The sensitivity of the test was calculated as the proportion of positive results (a score of 1+ or higher) in intestinal metaplasia samples. Specificity was calculated as the proportion of negative results in normal gastric tissue samples. Binomial exact 95% confidence intervals (95% CI) were calculated for sensitivities and specificities using Stata version 8.0 (Stata Corporation, College Station, TX).

Figure 1. Claudin-4 immunolabeling. A. Normal gastric mucosa, nonlabeling, with apposing 2+ labeled intestinal metaplasia. B to D. Gastric epithelial dysplasia, primary cancer, and metastatic cancer, respectively, showing 3+ immunolabeling. Magnification, ×100.
Results

Patients. Of the 436 gastric adenocarcinoma patients operated on at the Johns Hopkins Hospital from 1984 to 2002, 133 operated before December 1994 were selected for this study. Detailed characteristics of these 436 patients have been reported (22, 23). Briefly, the patients in the current study were predominately male (66%) with a median age at operation of 65 years. Pain, weight loss, and dysphagia were the most common presenting symptoms. Eighty-five (20%) cancers were stage I; 83 (19%) stage II; 145 (34%) stage III; and 117 (27%) stage IV. The primary tumors were distributed throughout the anatomic areas of the stomach: 26% in the antrum, 23% in the cardia, 7% along the lesser curvature, 5% in the body, 4% in the fundus, 4% in the pylorus, 2% along the greater curvature, and 30% elsewhere or overlapping in the stomach. The

Figure 2. MKK4 immunolabeling. A. Normal gastric mucosa, nonlabeling, with apposing 1+ labeled intestinal metaplasia. B to D. Gastric epithelial dysplasia, primary cancer, and metastatic cancer, respectively, showing 2+ immunolabeling in (B and C), and 1+ in (D). Magnification, ×40.

Figure 3. Stratifin immunolabeling. A. Normal gastric mucosa, nonlabeling, with apposing 2+ labeled intestinal metaplasia. B to D. Gastric epithelial dysplasia, primary cancer, and metastatic cancer, respectively, showing 2+ immunolabeling. Magnification, ×100.
Table 1. Claudin-4 immunolabeling of primary and metastatic gastric adenocarcinoma, normal stomach, and gastric intestinal metaplasia

<table>
<thead>
<tr>
<th>Score*</th>
<th>Normal stomach (n = 109)</th>
<th>Intestinal metaplasia (n = 36)</th>
<th>Dysplasia (n = 14)</th>
<th>Primary cancer (n = 125)</th>
<th>Metastatic cancer (n = 71)</th>
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<tr>
<td>0</td>
<td>93 (85%)</td>
<td>0</td>
<td>0</td>
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<td>All +</td>
<td>16 (15%)</td>
<td>36 (100%)</td>
<td>14 (100%)</td>
<td>123 (98%)</td>
<td>71 (100%)</td>
</tr>
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<td>0</td>
<td>8 (6%)</td>
<td>4 (6%)</td>
</tr>
<tr>
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<td>20 (56%)</td>
<td>3 (21%)</td>
<td>44 (35%)</td>
<td>28 (39%)</td>
</tr>
<tr>
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<td>1 (1%)</td>
<td>16 (44%)</td>
<td>11 (79%)</td>
<td>71 (57%)</td>
<td>39 (55%)</td>
</tr>
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</table>

*See text for description of scoring system.

MKK4. MKK4 immunolabeling results are shown in Table 2 and Fig. 2. Normal gastric mucosa distant from the primary cancer was available from 76 gastric adenocarcinoma patients on the tissue microarrays. Of these, only 6 (8%) showed MKK4 immunolabeling. All of those normal stomach samples with positive MKK4 labeling showed only moderate (1+) labeling.

There were 27 intestinal metaplasia and 12 gastric epithelial dysplasia lesions available for MKK4 immunolabeling on the tissue microarrays. In contrast to the normal mucosa, 89% of the intestinal metaplasia lesions and 100% of the gastric epithelial dysplasia lesions showed positive MKK4 immunolabeling. MKK4 labeling occurred in a cytoplasmic pattern. The labeling was generally moderate (1+), with a few more strongly labeling cases (2+). The labeling of the more advanced, gastric epithelial dysplasia, lesions in contrast was correspondingly more intense, with half the positive cases scoring strongly (2+) and half scoring moderately (1+), compared with the earlier, intestinal metaplasia, lesions, only 4% of which scored strongly (2+). The sensitivity and specificity of MKK4 to distinguish intestinal metaplasia from normal stomach were 89% (95% CI, 71-98%) and 92% (95% CI, 84-97%), respectively.

Of 124 primary cancers evaluated by MKK4 immunolabeling, 9 (7%) were scored 0, whereas 115 (93%) were scored 1+ (64%) and 2+ (28%). Seventy of the 73 metastatic lesions (96%) of the tissue microarrays showed positive MKK4 labeling. As with intestinal metaplasia and gastric epithelial dysplasia immunolabeling results, MKK4 labeling of the primary gastric adenocarcinoma and metastatic lesions occurred in a cytoplasmic pattern.

Stratifin. Stratifin immunolabeling results are shown in Table 3 and Fig. 3. Normal gastric mucosa distant from the primary cancer was available from 64 gastric adenocarcinoma patients on the tissue microarrays. Of these, only 2 (3%) showed stratifin immunolabeling. No cases of normal stomach with strong positive stratifin labeling (2+) were observed.

There were 30 intestinal metaplasia and 8 gastric epithelial dysplasia lesions available for stratifin immunolabeling on the tissue microarrays. In contrast to the normal mucosa, 97% of the intestinal metaplasia lesions and 100% of the gastric epithelial dysplasia lesions showed potential stratifin immunolabeling. Stratifin labeling occurred in a predominantly perinuclear and cytoplasmic pattern, but occasionally was membranous. The labeling of the intestinal metaplasia and

Table 2. MKK4 immunolabeling of primary and metastatic gastric adenocarcinoma, normal stomach, and gastric intestinal metaplasia

<table>
<thead>
<tr>
<th>Score*</th>
<th>Normal stomach (n = 76)</th>
<th>Intestinal metaplasia (n = 27)</th>
<th>Dysplasia (n = 12)</th>
<th>Primary cancer (n = 124)</th>
<th>Metastatic cancer (n = 73)</th>
</tr>
</thead>
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<tr>
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<td>70 (92%)</td>
<td>3 (11%)</td>
<td>0</td>
<td>9 (7%)</td>
<td>3 (4%)</td>
</tr>
<tr>
<td>All +</td>
<td>6 (8%)</td>
<td>24 (89%)</td>
<td>12 (100%)</td>
<td>115 (93%)</td>
<td>70 (96%)</td>
</tr>
<tr>
<td>1+</td>
<td>6 (8%)</td>
<td>23 (85%)</td>
<td>6 (50%)</td>
<td>80 (64%)</td>
<td>58 (80%)</td>
</tr>
<tr>
<td>2+</td>
<td>0</td>
<td>1 (4%)</td>
<td>6 (50%)</td>
<td>35 (28%)</td>
<td>12 (16%)</td>
</tr>
</tbody>
</table>

*See text for description of scoring system.
gastric epithelial dysplasia lesions was generally moderate (1+), with a few more strongly labeled cases (2+). The sensitivity and specificity of stratifin to distinguish intestinal metaplasia from normal stomach were 97% (95% CI, 0.83-0.99) and 97% (95% CI, 0.89-0.99), respectively.

Of 120 primary cancers evaluated by stratifin immunolabeling, 9 (8%) were scored 0, whereas 111 (93%) were scored 1+ (63%) and 2+ (29%). Of 71 metastatic lesions, 69 (97%) of the tissue microarrays showed positive stratifin labeling. As with intestinal metaplasia and gastric epithelial dysplasia immunolabeling results, stratifin labeling of the primary gastric adenocarcinoma and metastatic lesions occurred in a predominantly perinuclear and cytoplasmic pattern.

### Discussion

Gastric adenocarcinoma, like most other solid tumors, is thought to develop in a stepwise fashion. This pattern of carcinogenesis has been well described in the colon (24) and the pancreas (25), and will likely be described in greater detail in the stomach as well. As early as 1955, such a progression model was anticipated by Morson (2-4) who first described the transition from normal mucosa to intestinal metaplasia to gastric epithelial dysplasia to the development of gastric adenocarcinoma. More recently, distinctive patterns of gene expression in premalignant gastric mucosa and gastric cancer have been published (6), providing a framework for a gastric adenocarcinoma progression model. Our immunolabeling results are consistent with a progression model of gastric carcinogenesis insofar as the quantity (number of positive cases) and quality (intensity of labeling) generally increase from normal gastric mucosa to intestinal metaplasia to gastric epithelial dysplasia, primary cancers, and metastatic lesions. The exact molecular steps in the progression model analogous to colon and pancreas remain to be elucidated.

Intestinal metaplasia is not a single pathologic entity, but a spectrum of lesions ranging from normal mucosa to near-dysplastic mucosa. Classification schemes for intestinal metaplasia subtypes have been developed, typically dividing lesions into the categories complete and incomplete, based on the mucin content of the columnar-type and goblet cells (26, 27). Conflicting data exist regarding the prognostic significance of the subtypes. Studies from the 1980s and early 1990s suggested that the incomplete type carries a greater potential for malignancy (28-30) but recent studies have been more consistent with the notion intestinal metaplasia subtype is a poor predictor of future cancer risk (31). Intestinal metaplasia can occur anywhere in the stomach and, although there are differences between the gastric cardia and the stomach distal to the cardia, such as the increasing incidence of cardia lesions compared with distal tumors, intestinal metaplasia is considered to be premalignant in both the cardia (32) and the stomach distal to the cardia (33).

Claudins, together with occludin and junctional adhesion molecules, are the major components of intercellular tight junctions. These proteins function predominantly in paracellular transport and are expressed on both epithelial and endothelial cells. Overexpression of claudin proteins has previously been reported in invasive cancers derived from epithelial tissues. Although claudin-4 has been shown by gene expression profiling to be overexpressed in pancreas (9, 34), breast (10), ovarian (11, 12), and gastric cancers (7, 13), overexpression of claudin-4 has not, to our knowledge, been previously reported in intestinal metaplasia lesions associated with gastric adenocarcinoma.

Claudin-4 is a functional receptor for CPE receptor, and this characteristic has already been successfully exploited in cell lines and xenografts (16, 17). Another therapeutic possibility is that the fragment of CPE bound by claudin-4 could be attached to a cytotoxic substance for administration to patients with claudin-4-overexpressing tumors. However, the expression of claudin-4 on a variety of other, normal human tissues, including lung, liver, small and large bowel, and kidney, suggests that local delivery may be advantageous over systemic administration, where the dose-limiting toxicities may be prohibitive. The high sensitivity and specificity of anti-claudin-4 immunolabeling presented here, the observation that intestinal metaplasia reliably and robustly expresses claudin-4 in the cell membrane of gastric adenocarcinoma, intestinal metaplasia, and gastric epithelial dysplasia, and the claudin-4 homology to the CPE receptor suggests that local, topical approaches may indeed be feasible.

The biological significance of alterations in the expression of tight junction proteins in cancer is poorly understood. E-cadherin functions in intercellular adhesion and mutation of the gene is the most common genetic alteration known in diffuse-type gastric cancers, which display highly abnormal adhesion characteristics. Claudin is up-regulated in a variety of tumor types, but the causes and consequences of increased claudin expression in gastric cancer and its precursor lesions are poorly understood. Studies of mutations in the claudin genes, as well as investigation into their altered structure, subcellular localization, and function in gastric tumor may bring new insight into the role of claudin-4 in gastric adenocarcinoma pathogenesis.

**MKK4** (also known as \( JNK1 \), MAP2K4, and \( SEK1 \)), located on chromosome 17p11 proximal to the \( p53 \) tumor-suppressor gene, is thought to be a tumor-suppressor gene itself because it is mutated in \( \sim 4 \% \) of tumors of many types, e.g., pancreas, biliary, breast, and colon (35-37). MKK4 is a central mediator of the c-Jun-NH2-kinase cascade, whose members bear high homology with the related extracellular signal-regulated kinase and p38 cascades in the mitogen-activated protein kinase family. Activation of Ras can trigger a series of events whereby the extracellular signal-regulated kinase cascade sends a proliferative signal, but it can also activate the c-Jun-NH2-kinase pathway to cause apoptosis (38). Data regarding the role of MKK4 in carcinogenesis are conflicting. Despite the widely understood role of MKK4 as a tumor suppressor (35-37), Wang et al. (39) recently published evidence of MKK4 prooncogenic activity. Previous studies in our laboratory, using the same tissue microarrays as in the present study, revealed that a lack of tumor MKK4 expression correlated with decreased patient survival (22, 23) and, therefore, support a tumor-suppressive role.

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**Table 3. Stratifin immunolabeling of primary and metastatic gastric adenocarcinoma, normal stomach, and gastric intestinal metaplasia**

<table>
<thead>
<tr>
<th>Score</th>
<th>Normal stomach (n = 64)</th>
<th>Intestinal metaplasia (n = 30)</th>
<th>Dysplasia (n = 8)</th>
<th>Primary cancer (n = 120)</th>
<th>Metastatic cancer (n = 71)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>62 (97%)</td>
<td>1 (3%)</td>
<td>0</td>
<td>9 (8%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>All +</td>
<td>2 (3%)</td>
<td>29 (97%)</td>
<td>8 (100%)</td>
<td>111 (93%)</td>
<td>69 (97%)</td>
</tr>
<tr>
<td>1+</td>
<td>2 (3%)</td>
<td>24 (80%)</td>
<td>5 (62%)</td>
<td>76 (63%)</td>
<td>49 (69%)</td>
</tr>
<tr>
<td>2+</td>
<td>0</td>
<td>5 (17%)</td>
<td>3 (38%)</td>
<td>35 (29%)</td>
<td>20 (28%)</td>
</tr>
</tbody>
</table>

*See text for description of scoring system.*

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At first glance, it may seem counterintuitive that expression of a tumor suppressor like MKK4 is found to be a good marker of precursor lesions. One might expect that, instead, an oncogene would be more likely to serve this purpose. Nevertheless, it may be that in its role as a central mediator of the cell stress response, MKK4 is expressed in the progression toward intestinal metaplasia. Indeed, we have observed that sections of normal stomach that show histologic evidence or injury and repair show positive MKK4 immunolabeling, whereas quiescent samples of normal stomach do not. Consistent with the multistep model of GAC proposed by Morson (2-4) and by Correa (5), we might indeed expect that intestinal metaplasia has resulted from a progression through an initial insult like chronic gastritis and may consistently express stress-response proteins like MKK4, even in the absence of ongoing repair. Accordingly, we have eliminated cases of both normal stomach and intestinal metaplasia that have histologic evidence of ongoing repair and the ability of MKK4 to distinguish intestinal metaplasia from normal stomach persists.

Stratifin is a member of the 14-3-3 family of highly conserved dimer proteins that have thus far been shown to interact with over 100 other cellular proteins, predominantly those with a phosphoserine- or phosphothreonine-containing motif, suggesting a role as a general biochemical regulator (reviewed in refs. 40-42). Indeed, 14-3-3 proteins participate in such diverse cellular processes as cell cycle progression, apoptosis, signal transduction, stress response, cytoskeleton organization, and viral and bacterial pathogenesis. Given the staggeringly wide array of cellular functions involving such ubiquitous proteins, speculation regarding the specific role of stratifin in gastric carcinogenesis is premature. In fact, there are conflicting reports on level of activation of stratifin in cancers of various organs. For example, stratifin expression is reported to be up-regulated in some pancreas (43, 44), lung (45), and head-and-neck (46) carcinomas, but down-regulated in other breast (47), prostate (48), liver (49), and squamous cell carcinomas (50, 51). Interestingly, but consistent with the promiscuity of stratifin, we observed stratifin immunolabeling in a variety of patterns, including perinuclear, cytoplasmic, and, in gastric epithelial dysplasia, membranous.

Other markers of gastric intestinal metaplasia have been reported, including the Das-1 monoclonal antibody (52) and liver-intestinal cadherin (53). Grotzinger et al. studied 30 patients of whom only 12 had intestinal metaplasia, and in all cases of intestinal metaplasia, liver-intestinal cadherin staining was positive. The small sample size, however, makes meaningful interpretation difficult. Mirtz et al. studied the ability of the Barrett’s epithelium marker Das-1 to detect gastric intestinal metaplasia and found positive immunolabeling of intestinal metaplasia in 35% of noncancer patient samples and in 93% of cancer patient samples. Claudin-4 has the advantage of higher sensitivity (100%), and combined with MKK4 and stratifin, the specificity also approached 100%. Furthermore, claudin-4 has a clear therapeutic approach through the well-characterized homology to the CPE receptor.

In conclusion, we present a panel of three markers identifying the gastric adenocarcinoma precursor lesions intestinal metaplasia and gastric epithelial dysplasia. The combination of claudin-4, MKK4, and stratifin immunolabeling may provide nearly 100% sensitivity and specificity in identifying gastric adenocarcinoma precursor lesions. Currently, only claudin-4, on the basis of the CPE receptor homology, has an immediate possibility for diagnostic and therapeutic application in patients. However, because all three have a reasonable sensitivity and specificity, it may be possible to design labeled antibodies that could be applied endoscopically, without invasive biopsy, and then detected during the same endoscopy as they identify gastric adenocarcinoma precursor lesions. Furthermore, compared with chromoendoscopic methods using vital dyes that have been associated with DNA damage (54), a labeled antibody solution may be comparatively less genotoxic. For example, for patients with increased risk of gastric cancer, such as those with dietary, racial, or familial risks of gastric adenocarcinoma or those who have had a resection of gastric adenocarcinoma, the ability to detect asymptomatic precursor lesions may have therapeutic benefit. Further clinical studies are warranted to evaluate these markers, both in cancer patients at risk for gastric adenocarcinoma recurrence after resection, and in high-risk patients who do not yet have a diagnosis of cancer.

References
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