Helicobacter pylori as a crucial factor in intestinal metaplasia development of gastric mucosa

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Abstract: Helicobacter pylori (H. pylori) is detected on the surface of gastric epithelium and in goblet cells, predominantly in patients with chronic atrophic gastritis and incomplete intestinal metaplasia (IM). H. pylori infection persistence leads to the formation of gastrointestinal phenotype of IM. H. pylori can be considered as an etiological factor of IM. It inhibits the expression of SOX2 in gastric epithelial cells, hence activating transcription factor CDX2 as a counterpart to MUC5AC gene inhibition and MUC2 gene induction. Thus, in metaplastic cells, programming differentiation after intestinal phenotype will develop. The role of H. pylori in the origin of intestinal metaplasia of gastric mucosa was defined in this study to elucidate the probable mechanism of cell reprogramming. The activation of CDX2, with simultaneous inactivation and decreased number of genes (e.g., SHH, SOX2, and RUNX3) responsible for gastric differentiation, was identified to cause the appearance of IM.

Keywords: Helicobacter pylori; intestinal metaplasia; gastric mucosa

Citation: Vernygorodskyi S. Helicobacter pylori as a crucial factor in intestinal metaplasia development of gastric mucosa. Adv Mod Oncol Res 2016; 2(3): xx–xx; http://dx.doi.org/10.18282/amor.v2.i3.72.

Received: 27th October 2015; Accepted: 09th March 2016; Published Online: 08th June 2016

Introduction

Helicobacter pylori (H. pylori) is the most frequent cause of gastritis, classified by the International Agency for Research on Cancer (IARC) as type I (definite) human carcinogen in 1994[1]. Two proposed mechanisms in the carcinogenic cascade are the immune response elicited by H. pylori and the damage resulting from oxidative stress[2]. Multifocal atrophic gastritis and intestinal metaplasia confer a high risk of developing gastric cancer and are considered to be pre-cancerous conditions[3]. Mucins, a type of glycoproteins, lubricate and protect epithelial surfaces in addition to supporting epithelial integrity. Gastric mucins (MUC5AC and MUC6) are typically detected in a cell-specific expression pattern in normal mucosa[4]. In contrast, intestinal mucins (MUC2 and MUC4) are detected in gastric adenocarcinomas and during the initial stages of neoplastic transformation[5].

Meanwhile, caudal-type homeobox 2 (CDX2) is a transcription factor member of the caudal-related homeobox gene family responsible for intestinal epithelial development[6], which is expressed in small intestinal and colonic epithelia but not in gastric epithelium under normal conditions. However, gastric epithelial cells could potentially acquire ectopic expression of CDX2 and transdifferentiate into an intestinal phenotype (intestinal metaplasia) when normal gastric mucosa environment is irritated by H. pylori infection[7].

H. pylori is a leading cause of transdifferentiation into intestinal metaplasia, which could potentially manifest as gastric cancer. Nonetheless, the molecular pathogenesis of this transdifferentiation process has not been extensively studied[8]. The aim of this work was to define the role of H. pylori in the origin of intestinal metaplasia of gastric mucosa and to elucidate the probable mechanism of cell reprogramming.
Materials and methods

Study population

Between 2009 and 2014, 182 patients who were sent to endoscopy departments in hospitals within Vinnytsya were examined. There were 96 male (53%) and 86 female patients (47%): 30 patients with normal gastric mucosa, 30 with chronic atrophic gastritis (CAG) without intestinal metaplasia (IM), 68 with CAG and IM, and 54 with gastric cancer (Table 1). Among these patients, we selected 68 patients with CAG and IM as the main group for further investigation since IM is closely associated with this disease. In this group, 42 patients were diagnosed as H. pylori-infected and 26 patients tested negative for H. pylori. In the non-infected patients, the etiology for 6 of the 26 CAG patients was considered as chemical due to gastroduodenal reflux, and was unknown in the remaining 20 CAG patients.

The comparison group included 30 patients with CAG without IM (16 H. pylori-infected and 14 non-infected). In the non-infected group, the etiology in four CAG patients was chemical due to gastroduodenal reflux and in the remaining 10 patients, the causes were not identified (e.g., chemical, autoimmune or other causes).

The average patient age was 52.96 ± 1.13 and the average duration of the disease from the date of IM diagnosis was 2.6 ± 0.63 years. The average duration of the disease was identified from the first diagnosis of IM confirmed by histological method. As a first-line therapy for H. pylori eradication, all patients were given a 10-day triple therapy with omeprazole (20 mg, twice daily), amoxicillin (1 g/day) and/or metronidazole (500 mg, twice daily). In 14 of the 16 H. pylori-infected patients with CAG without IM, this therapy was effective and no changes in the stages of CAG were observed. However, infection persistence was observed in two patients with CAG, and it transformed from stage 2 to stage 3.

In 27 of the 42 H. pylori-infected patients with CAG and IM, eradication therapy was also effective and no changes were observed. However, in 15 patients, infection persistence caused stages of atrophy to change (CAG transformed from stage 2 to 3 in five patients, and from stage 3 to 4 in seven patients, during the six-year follow up).

In addition, surgical specimens of gastric adenocarcinoma as well as the adjacent mucosa were investigated. A total of 54 patients were enrolled into the study: 28 adenocarcinoma, 12 signet-ring cell carcinoma, and 14 undifferentiated tumors. A distribution of the 54 patients according to TNM staging is given in Table 2.

| Table 1. Clinicopathological characteristics of patients with chronic atrophic gastritis and intestinal metaplasia |
|--------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| Normal gastric mucosa (N = 30) | Chronic atrophic gastritis (N = 30) | Chronic atrophic gastritis with intestinal metaplasia (N = 68) |
| Mean age (Years) | 46 | 53 | 52 |
| Male/Female | 20/10 | 18/12 | 26/14 |
| Helicobacter pylori (+)/(−) | - | 16/14 | 11/17 |

| Table 2. Distribution of patients with cancer of the stomach according to TNM staging |
|---------------------------------|-----------------|-----------------|
| Stage | Number of patients | % |
| | N | |
| Ia | (T₁N₀M₀) | 4 | 7.4 |
| Ib | (T₁N₀M₀) | 21 | 38.9 |
| II | (T₂N₀M₀) | 12 | 22.2 |
| IIIa | (T₁N₀M₀) | 4 | 7.4 |
| IIIb | (T₂N₀M₀) | 4 | 7.4 |
| IV | (T₂N₀M₀) | 2 | 3.7 |
| | (T₂N₁M₀) | 3 | 5.5 |
| | (T₂N₂M₀) | 1 | 1.9 |
| | (T₂N₂M₁) | 1 | 1.9 |
| Total | 54 | 100% |

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Biopsies

Multiple biopsies were performed during endoscopy and chromoendoscopy using 0.5% methylene blue. Two biopsies were done from the lesser and greater curvature of the body and antrum, and one from an area at an angle of the stomach, all while taking into account the requirements of the modified Sydney system of chronic gastritis diagnosis and the stained areas of gastric mucosa following histological study of the biopsies. Biopsy materials were processed via conventional histological methods.

To define metaplastic changes of the gastric mucosa, the following methods were used: staining with hematoxylin, eosin, and van Gisone combined with high iron diamine and alcin blue; orsein combined with alcin blue; Gomory aldehyde fuchsia; and alcin blue at pH 1.0 and pH 2.5 together with periodic acid Schiff (PAS) reaction. H. pylori persistence was tested using rapid urease test, 13C urea breath test with Pappenheim stain, as well as with Romanovsky-Giemsa and toluidine blue staining. In order to evaluate the degree of bacterial contamination, we used a quantitative method (the number of H. pylori was calculated under high microscope magnification and the degree of contamination was classified: up to 20 bacteria as weak (+), from 20 to 50 as moderate (++), and more than 50 as marked (+++).

Immunohistochemical studies

Immunohistochemical studies were conducted in paraffin sections using streptavidin-biotin visualization method (Dako, Denmark). Antigen de-masking was carried out in citrate buffer at pH 6.0. Mouse and rabbit monoclonal antibodies (mAb) were used as initial antibodies. Cell nuclei were counterstained with Mayer hematoxylin for 15–60 s. CDX2 expression was estimated using mouse mAb to nucleus antigen CDX2 and mAb clone DAK-CDX2 (Dako, Denmark). Mucin profile was determined using MUC5AC, MUC2 and MUC6 antibodies (clones CLH2, Ccp58 and CLH5) (Novocastra, United Kingdom).

In preparation for the 400-fold microscope magnification, we determined the intestinal differentiation index (nucleus mark CDX2) in five arbitrarily selected fields of vision (≤500 cells) as a portion in a percentage of the positively stained epithelial cell nuclei of gastric mucosa in three compartments (I: surface and fossa epithelium; II: isthmus zone; III: basal, middle and lower third of glands to basal sections). To estimate mucin expressions (MUC5AC, MUC2, and MUC6) in the gastric mucosa of the same sections, we used semi-quantitative estimation scale of staining intensity: ‘0’ (absent), for absence of positive reaction in cells; ‘1’ (weak), up to 30% of cells reacted positively; ‘2’ (moderate), 31%–60% positive reaction; and ‘3’ (strong), ≥60% stained cells.

Statistical analyses

Results of immunohistochemical alterations were compared to clinicopathological features using chi-square test with two-tailed p value, where p < 0.05 was considered as significant.

Ethics statement

All patients were thoroughly informed about the study which was approved by the local ethics committee.

Results

The highest incidence of H. pylori was revealed in CAG with incomplete intestinal metaplasia (IIM). Among the 42 infected patients with IM, bacterium was identified in 73% of CAG patients with IIM (Figure 1, Tables 3 and 4).

H. pylori’s depth of penetration in the gastric mucosal structure was directly proportional to the degree of pathological changes. Its location on the surface of the gastric mucosa and glands in the body was often combined with complete intestinal metaplasia (CIM) in 52% of the patients. However, intraepithelial localization of the microorganisms, particularly in the cytoplasm of goblet cells of metaplastic epithelium, was observed in 91% of patients with IIM in the antrum (Figure 2). In addition, gastric mucosa epithelial cells around the IIM were observed with cellular dysplasia. Given the critical role of H. pylori in the onset and progression of atrophy in patients with CAG, we analyzed the incidence of IIM in infected patients depending on the degree of contamination (Figure 3).

IIM prevalence was significantly observed (p < 0.05) in H. pylori positive (+) CAG patients with moderate and strong degree of bacterial contamination.
Helicobacter pylori as a crucial factor in intestinal metaplasia development of gastric mucosa

### Table 3. Detection rate and degree of contamination of *H. pylori* in patients with CAG and IM

<table>
<thead>
<tr>
<th>Type of CAG</th>
<th>Total</th>
<th><em>H. pylori</em> (–)</th>
<th><em>H. pylori</em> (+)</th>
<th>Degree of gastric mucosa contamination</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Weak (+)</td>
</tr>
<tr>
<td>CAG with CIM</td>
<td>28</td>
<td>17 (65)</td>
<td>11 (27)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>CAG with IIM</td>
<td>40</td>
<td>9 (35)</td>
<td>31 (73)</td>
<td>4 (13)</td>
</tr>
<tr>
<td>Total</td>
<td>68</td>
<td>26</td>
<td>42</td>
<td>5</td>
</tr>
</tbody>
</table>

CAG: chronic atrophic gastritis; CIM: complete intestinal metaplasia; IIM: incomplete intestinal metaplasia

### Table 4. Detection rate and degree of contamination of *H. pylori* in patients with CAG without IM

<table>
<thead>
<tr>
<th>Type of CAG</th>
<th>Total</th>
<th><em>H. pylori</em> (–)</th>
<th><em>H. pylori</em> (+)</th>
<th>Degree of gastric mucosa contamination</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Weak (+)</td>
</tr>
<tr>
<td>CAG without IM</td>
<td>30</td>
<td>14 (47)</td>
<td>16 (53)</td>
<td>6 (37.5)</td>
</tr>
</tbody>
</table>

### Figure 2. Intraepithelial localization of *Helicobacter pylori* within goblet cells. Incomplete intestinal metaplasia, Romanovsk-Giemsa, magnification: 1000X.

marked degree of bacterial colonization of the gastric mucosa, in comparison to *H. pylori* negative (–) patients. In addition, the incidence of IIM in *H. pylori* (+) patients depended on the degree of gastric mucosa colonization. Percentage of patients with severe degree of infection (+++) was 21%, significantly higher (p < 0.05) than those with a low degree of contamination (9.5%).

The identification of CIM and IIM depending on the degree of *H. pylori* contamination of the gastric mucosa can be regarded as an evidence of the causal relationship between *H. pylori* and IM on the progression of gastric mucosa reconstruction in patients with CAG. Furthermore, it has been suggested that there was an increase of both types of IM in patients with more active gastritis and a prevalence of IIM in patients with moderate and severe CAG, in comparison with CIM.

In all patients with normal mucosa and CAG without IM, expression of CDX2 was absent. CIM in patients with CAG was characterized by a high level of CDX2 expression with goblet cells nuclei and columnar epithelia along the brush border (Figure 4). During histochemical analysis of goblet cells, we found a presence of acidic sialomucin and a predominance of intestinal mucin MUC2. We also detected the absence of neutral glycoproteins, acidic mucus (sialomucin and sulfomucin) and MUC5AC in columnar epithelial cells. Patients with CIM and *H. pylori* infection had higher levels of CDX2 expressions which was 0.89 ± 0.01 (p < 0.001) (Table 5), in comparison to the *H. pylori* (–) group.

The expression of MUC5AC had not been defined in columnar epithelocytes surrounding CIM despite strong and moderate expression in areas with IIM. In the *H. pylori* (–) group associated with CAG, MUC5AC labeling was moderate and weak. After eradicating *H. pylori* infection, the expression of MUC5AC was amplified. MUC5AC expression in columnar epithelial cells was detected in the cytoplasm and membranes of goblet cells of 21% IIM patients. In patients with a long history of CAG (over three years) and over six years in a group subjected to dynamic monitoring, the loss of MUC5AC was observed in 34% patients of incomplete IM with severe and mild dysplasia (Figure 5).

A decrease of mucin-positive cells was visible in areas of incomplete IM adjacent to cancer and in neoplastic
Figure 3. Rate of IM in patients with CAG depending on the degree of contamination of *H. pylori* on the gastric mucosa

Figure 4. Marked expression of intestinal transcription factor CDX2 in the nuclei of gastric epithelial cells, goblet, and columnar epithelial cells with brush border. Immunohistochemical marking of CDX2, magnification: 100X

cells. In 37% (20 of 54) of patients with gastric cancer, MUC5AC expression remained in the IM areas adjacent to cancer IM and in neoplastic cells, which may predominantly indicate gastric type adenocarcinoma (Figure 6). It should be noted that the loss of mucin-producing properties was observed mainly in patients with poorly differentiated adenocarcinoma; however, in 44% of patients with cancer signet-ring cells carcinomas, MUC5AC labeling remained. MUC2 expression was moderate in the cytoplasm, sometimes heavily expressed in the membranes of goblet cells, and remained in CIM and IIM cases. In the initial phases of secretion, goblet cells were wedge-shaped with the apex directed toward the basal parts and with the foundation directed toward the lumen of the stomach. In areas adjacent to adenocarcinoma in metaplastically modified cells, we observed weak expression of MUC2. During the observation, we found no positive labeling of MUC2 in the group of patients with gastric signet-ring cell cancer.

MUC6 expression was observed mainly in pyloric exocrinocytes within the deeper parts of the lamina propria. Expression was moderate in areas of incomplete IM and those lacking in complete IM. Thus, the intensity of MUC6 expression would depend on the spread of IM, indicating a progressive displacement of pyloric glands with neogenic intestinal epithelium and severe IM (stage

**Table 5.** CDX2 expression of patients with chronic atrophic gastritis and intestinal metaplasia (M ± m)

<table>
<thead>
<tr>
<th>Nosology</th>
<th>Expression level of CDX2 in groups of patients</th>
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<tbody>
<tr>
<td></td>
<td><em>H. pylori</em>(+)</td>
</tr>
<tr>
<td>Normal</td>
<td>–</td>
</tr>
<tr>
<td>CAG with CIM</td>
<td>0.89 ± 0.01</td>
</tr>
<tr>
<td>CAG with IIM</td>
<td>0.24 ± 0.06&lt;sup&gt;**&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

(+): positive gastritis; (–): negative gastritis; CAG: chronic atrophic gastritis; CIM: complete intestinal metaplasia; IIM: incomplete intestinal metaplasia; <sup>*</sup>p < 0.001 to *H. pylori* (+); <sup>**</sup>p < 0.001 to CIM
Helicobacter pylori as a crucial factor in intestinal metaplasia development of gastric mucosa

Figure 5. Loss of MUC5AC expression in the foveolar epithelium areas of IIM and dysplasia in patients with CAG and IIM. Immunohistochemical staining of MUC5AC, magnification: 400X

Figure 6. Moderate MUC5AC expressions in tumor cells with poorly differentiated stomach adenocarcinoma; epithelial cells of gastric mucosa with CAG, and IIM. Immunohistochemical staining of MUC5AC, magnification: 100X

3 of chronic atrophic metaplastic gastritis). While studying biopsies from the fundus, we had noted positive labeling of MUC6 in exocrinocytes of the oxyntic glands, confirming its restructuring and development of pyloric metaplasia (pylorization), with increased MUC6 in surface mucous cells of H. pylori (+) patients.

After eradicating H. pylori, the number of gastric epithelial cells with CDX2-positive nuclei decreased. This indicated a possible warning of gastric mucosa epithelium nucleus reprogramming if infection was eradicated in time. We also asserted that CDX2 expression in the nuclei of columnar cells in sections of CIM was not affected by the eradication of the infection, indicating the attachment of intestinal phenotype of metaplasia epithelium. IIM is characterized by weaker expression of CDX2 transcription factor concerning CIM, yet 75% of the patients did not have it. At the same time, in sections of intestinal metaplasia with dysplastically changed epithelium, we observed CDX2 expression disappearing.

When we compared the results of patients with CAG from the H. pylori (-) and H. pylori (+) groups, we found that focally expressed positive immunohistochemical reactions dominated the results of infected patients. The absence of CDX2 in gastric mucosa epithelial cell nuclei in sections attached to cancerous growth was a typical phenomenon in 98% of test subjects. At the same time, CDX2 expression was lacking in cases of complete and incomplete intestinal metaplasia and was not correlated with the presence/absence of helicobacteriosis (p > 0.05). In the group of patients with gastric cancer, there were only two patients with moderately differentiated adenocarcinoma and weak CDX2 expression, but these were absent in the attached sections with intestinal metaplasia. We did not identify CDX2 marking in 96% of patients with low-differentiated adenocarcinoma and gastric epithelial cells. CDX2 in affected sections was negative in patients long suffering from intestinal metaplasia (more than 3–4 years), mostly of the incomplete type, regardless of H. pylori infection.

The presence of CDX2 in epithelial cell nuclei of gastric mucosa proved the formation of so-called gastrointestinal phenotype of epithelial cells. It is typical that between CDX2-positive goblet cells synthesizing intestinal mucin MUC2 and gastric mucin MUC5AC, there are CDX2-positive and CDX2-negative epithelial cells. MUC5AC expression, acidic mucins (sialomucin and sulfomucin) as well as neutral mucins can be detected by routine multicolored histochemical methods, and cellular phenotypic changes can serve as early markers for the emergence of intestinal metaplasia. Vivid CDX2 expression in goblet cells and columnar epithelial cells of CIM sections indicates both the end of metaplasia and the attachment of intestinal phenotype of epithelial cells.

When CDX2 expression increases, intestinal metaplasia is complete. This indicates the absence of gastric mucin (MUC5AC-positive) expression in columnar cells and striped edging will emerge. According to Dimmler et al., the gastric factor Sonic hedgehog (SHH) differentiation expression also disappears. At the same time, when CDX2 expression decreases, stomach glandular epithelium shows mixed phenotypic characteristic (gastrointestinal or incomplete intestinal metaplasia). Secretion of neutral glycoprotein produces sulfomucins in columnar epithelial cells. These types of intestinal meta-
plasia (such as type III and incomplete large intestinal) are more often found in cases of long (>2–4 years) atrophic changes of gastric mucosa in patients with *H. pylori* and according to findings in this study, are the most typical observation for chronic atrophic pangastritis.

It is also necessary to distinguish gastrointestinal phenotype of intestinal metaplasia originating from the persistence of helicobacteriosis. Gastrointestinal phenotype separation of intestinal metaplasia is rather significant for further treatment and prognosis of intestinal metaplasia. We proposed an algorithm for the management of patients with CAG depending on CDX2 expression (Figure 7):

![Figure 7. Determination of transcriptional factor CDX2. GE: gastric epitheliocytes; CC: columnar cells; GC: goblet cells. Standard scheme: alternating X-ray and fibrogastroendoscopy with multiple biopsies of the gastric mucosa and histopathological diagnosis of any focal pathology. Frequency of observations: once in two years for those aged 35–49 years old, annually for persons older than 50](image)

### Discussion and conclusion

The disorder of a family of regulation transcription factors such as SOX2, CDX2, PDX1, SHH, and OCT1 are important for embryonic tissue development and in transdifferentiation of fundal and pyloric exocrinocytes into intestinal epithelium. One of the factors directly influencing transcription factor function is *H. pylori*. SOX2 is regulated by interleukin 4 (IL-4) through the activation of transcription factor STAT6 (Signal Transducer and Activator of Transcription) in the gastric epithelium. This regulation can be directly suppressed by *H. pylori*. Under the influence of *H. pylori*, the differentiation of intestinal transcription factor CDX2 in gastric epithelial cells is activated, and MUC5AC as well as MUC2 are inhibited. The loss of CDX2 marking in the sections of intestinal metaplasia (complete and incomplete) can be an unfavorable prognostic peculiarity of malignization, since these changes indicated disorders of cell differentiation and tendencies to oncotransformation. Therapeutic intervention may be possible if IM of the stomach is reversible; otherwise, efforts should be directed at the prevention of the disease.

Intestinal metaplasia of the gastric mucosa is irreversible while intestinal phenotype of epithelial cells (completely formed goblet cells) are attaching. According to data in this study, intestinal metaplasia reoccurrence is possible in the case of gastric epithelial cell nuclei reprogramming until the completion of cell differentiation. Results in this study, which showed that *H. pylori* positive patients exhibited an increase in MUC6 in surface mucous cells with a reduction in MUC5AC, coincided with the findings of Reis et al. and Byrd et al.. Eliminating the infection leads to a regeneration of normal gastric pattern. The reversal of such expression has no explicitly known benefits as neither of these gastric MUC gene products have been isolated in their pure form. The expression of MUC5AC is reduced whereas the *de novo* expression of MUC2 occurs in gastric cancer. As the disease progresses, the expression of MUC5AC further reduces, but that of MUC2 decreases. In general, isolated MUC2 expression (the intestinal phenotype) correlates with metastatic progression and poor survival.

Considering data from literature, the absence of CDX2 marking in 96% patients with stomach cancer confirmed the anti-oncogenic properties of this transcription factor. Similar CDX2 properties were observed in colorectal adenocarcinomas. Thus, the marking of transcription factor CDX2 can be widely used for early intestinal metaplasia diagnosis and gastric mucosa oncotransformation. The suppositions concerning anti-oncogenic properties of this transcription factor need further studying.

*H. pylori* and the bone morphogenetic protein (BMP) pathway regulate CDX2 and SOX2 expression in gastric cells. These observations are largely derived from transgenic mouse model studies, in which CDX2 was controlled by promoters from different gastric specific...
Helicobacter pylori as a crucial factor in intestinal metaplasia development of gastric mucosa

genes (Foxa3 or H+/K+- ATPase b-subunit). According to Mutoh et al. and Silberg et al., the ectopic expression of CDX2 in the gastric mucosa of transgenic mice induced a complete transformation of the gastric mucosal glands to intestinal-like mucosa, thus verifying the role of CDX2 in intestinal differentiation17-18. Mutoh et al. also reported that invasive gastric carcinoma was caused by a long-term intestinal metaplasia of the CDX2 transgenic mice19. Part of this abnormal CDX2 expression is manifested in gastric dysplasia and gastric cancers19-21. Interestingly, recent investigations revealed that CDX2 expression has decreased in gastric dysplasia and cancer, even though Kim et al. claimed that a positive correlation exists between CDX2 expression and the grade of dysplasia and carcinoma22.

Other studies have reported a significantly reduced CDX2 expression in IIM compared to CIM, along with an inverse relationship between CDX2 expression in gastric cancer and the expression of MUC5AC and MUC623. In addition, CDX2- positive tumors have a better prognosis than CDX2-negative tumors, showing lower invasiveness, fewer lymph node metastases and a higher five-year survival rate3. Therefore, CDX2 is believed to be a tumor suppressor in human gastric carcinogenesis3. Regarding intestinal metaplasia, cellular biological peculiarities of epithelial cells depend not only on the type but also background processing character in gastric mucosa. Hence, differentiated approach based on the usage of molecular biological markers for intestinal metaplasia is not only of scientific interest but is also a fundamental basis for the development of methodical approaches in the prognosis and treatment of patients with intestinal metaplasia of gastric mucosa23.

Thus, results from molecular biological studies showed that CDX2 can attach intestinal phenotypes to cells and activate its own promoter, although this contradicts the concept of metaplasia reoccurrence. Further studies on this phenomenon would have to explain whether molecular mechanisms related to the emergence of intestinal metaplasia are identical during different pathological processes.

References


