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Methylation of the Estrogen Receptor Promoter in the Development of Gastric Carcinoma

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Introduction: Gastric carcinogenesis is a multistep process including mutation of different genes as well as epigenetic events as aberrant promoter methylation leading to gene silencing. Morphologically, disease progression appears as a sequence of intestinal metaplasia - dysplasia - invasive carcinoma, triggered by Helicobacter pylori (HP) infection. Methylation of the Estrogen receptor (ER) promoter has been attributed to the development of colorectal cancer and esophageal adenocarcinoma. Its role in gastric carcinogenesis has remained so far elusive.

Methods: To study Estrogen promoter methylation patterns along the carcinogenesis pathway in the stomach, we examined gastric mucosa in different conditions by quantitative methylation-specific PCR (q-MS). We tested samples from 8 newborns, 49 individuals with gastric cancer, and 8 newborns, 49 individuals with HP positive gastritis. Three specimen of this group showed positive q-MS. PCR specimens were analyzed blind and later correlated with histopathological findings. Results: None of the 8 newborns showed a positive q-MS. We tested samples from 8 newborns, 49 individuals with HP positive gastritis (11%). On the other hand, all individuals with HP pylori gastritis, intestinal metaplasia and gastric carcinoma were highly significant. Discussion: ER promoter methylation has been reported in the context of esophageal and colon carcinogenesis. Here we demonstrate that this epigenetic event is not tumor specific but already present in precancerous lesions of gastric cancer, as early as HP positive gastritis. This data suggests that ER promoter methylation might play a role in the early steps of gastric carcinogenesis and possibly can identify individuals at risk for this highly prevalent tumor.

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Stomach Cancer Risk in Gastric Cancer Relatives: Interaction Between Helicobacter pylori Infection and Family History of Gastric Cancer for the Risk of Stomach Cancer

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Goals: To identify the risk of gastric cancer in first-degree relatives of gastric cancer patients, and to determine if there is an interaction between H. pylori infection and family history of gastric cancer in gastric carcinogenesis. Background: It is unclear to what degree a family history of gastric cancer is associated with stomach cancer risk in Korea. Study: From May 2003 to July 2008, 428 gastric cancer patients and 368 controls were included in the analyses. Logistic regression models including age, gender, family history of gastric cancer, residence during childhood, smoking, monthly income, spicy food diet and H. pylori status were evaluated to estimate the odds ratios (ORs) of developing gastric cancer. Results: Adjusted OR for gastric cancer increased 3-fold for subjects reporting first degree relatives with gastric cancer (OR 2.85, 95% CI: 1.83-4.60). The association was strong in the 40 - 50 age group (OR 4.00, 95% CI: 2.06-7.76), and became weaker in subjects older than 50 years of age (OR 1.81, 95% CI: 0.93-3.46). Compared to the uninfected subjects without a family history, subjects with both a family history and H. pylori infection had a 5-fold increased risk (OR 5.32, 95% CI: 2.78-10.25). Conclusions: After adjusting for environmental factors and H. pylori infection, a family history of gastric cancer remained a risk factor associated with gastric cancer. The interaction between H. pylori infection and family history of gastric cancer might be a rationale for H. pylori eradication in the gastric cancer relatives as a strategy to prevent gastric cancer.

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CDX2 Autoregulation in Gastric and Intestinal Cell Lines

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Intestinal metaplasia (IM) of the stomach is associated with an increased risk of gastric carcinoma and consists in the transdifferentiation of gastric epithelial cells to an intestinal phenotype. This intestinal differentiation, both in normal and aberrant locations, is dependent on the presence of the homeobox gene CDX2. In normal conditions CDX2 is only expressed in the adult intestine but several studies, including our own, have shown that CDX2 is strongly expressed in human intestinal metaplastic lesions of the stomach, oesophagus, liver and gallbladder. Moreover, it was shown in a mouse model that CDX2 expression in the stomach was sufficient for the development of IM. The molecular mechanisms that regulate CDX2 expression are yet mostly unknown. We have recently shown that elements of the BMP/SMAD4 pathway not only co-localized with CDX2 in IM but also regulate CDX2 expression in gastric cell lines. Furthermore, it has been reported that CDX2 transactivates its own promoter In Vivo. The autoregulatory mechanism could be very important in IM establishment and maintenance. Hence we studied the putative regulation of CDX2 expression by the CDX2 protein. We show that CDX2 is able to transactivate a 3 kb fragment of the mCDX2 promoter, to different extents, in a panel of both gastric and intestinal cell lines, using promoter assays. Further, we demonstrate that CDX2 is bound to at least 3 different sites on its proximal 1.7 kb promoter in a living gastric carcinoma cell line. Finally, when transfecting cell lines with an exogenous CDX2-expressing vector, we found increased expression of its endogenous counterpart, and, concomitantly, an activation of its expression in HeLa cell line, which does not express CDX2. Altogether, this results show that CDX2 is able, in fact, to autoregulate its expression In Vivo. Further studies are needed to elucidate if this regulatory pathway may be important In Vivo as well.

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Clinicopathological Features and Prognostic Factors of Proximal Gastric Carcinoma in High H. pylori Prevalence Country; a Single Center, Large Volume Experience

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Background: The incidence of gastric cancer has fallen recent decades. Since the 1970s, both a substantial reduction in H. pylori prevalence and a substantial increase in the incidence of proximal gastric cancer (PGC) have been observed in the Western world and in Japan but not in other East Asian countries. The purpose of this large volume study was to analyze the clinicopathological features of PGC compared to other site of gastric cancer in Korea, a country with high H. pylori prevalence. We also investigated the factors affecting prognosis of PGC and compare survival between proximal and middle or distal gastric cancer. Methods: Between 2000 and 2005, 3,362 patients with gastric cancer were enrolled in this study. Patients involving the entire stomach were excluded (169 patients). The clinicopathological parameters along with respective survival data were analyzed comparing findings in patients with PGC and those with middle or distal gastric carcinoma (DGC). Results: Chronological analysis showed increasing incidence of PGC over the study period. PGC patients were younger and Bormann type III & IV were more common than DGC patients. Also, PGC patients were significantly associated with higher proportion of poorly differentiated type, T3 & T4 stage, positive lymph node compared to DGC patients. Pattern of metastasis of AGC was different according to the location. Peritoneal and other distant metastasis were significantly higher in PGC group compared to DGC group. The 5 year survival rate for PGC was 59.6% and that of DGC was 73.7% (p<0.001). In curatively resected patients, the 5-year survival rate was significantly lower in PGC than DGC. Also N0 and N1 category significantly influenced the 5 year survival rate. Tumor stage, hepatic metastasis and curative resection was the significant prognostic factors in PGC patients. However, increasing in incidence with respective decline in H. pylori prevalence in Korea. The five year survival was worse for patients with PGC than for those with DGC regardless of curative respectability. PGC is diagnosed in more advanced stages and special attention should be warranted for early detection.