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Lecture

A Causal role of *Helicobacter pylori* infection and eradication therapy in gastric carcinogenesis

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SUMMARY

Gastric cancer not located in the cardia still remains the second most common cancer worldwide, whereas adenocarcinoma of the cardia and gastroesophageal junction has been rapidly rising over the past two decades. Gastric cancer can be subdivided into diffuse and intestinal pathologic entities that have different epidemiologic and prognostic features. Various genetic and environmental factors lead to either abnormal genes overexpression or inappropriate expression of normal genes, whose products confer the malignant phenotype. Advances have been made in the genetic changes mostly of the intestinal type; its development is probably a multistep process, as has been well described in colon carcinogenesis. The most common genetic abnormalities tend to be loss of heterozygosity of tumor suppressor genes, particularly of p53 or "Adenomatous Polyposis Coli" gene. The latter leads to gastric oncogenesis through changes related to E-cadherin-catenin complex, which plays a critical role in normal tissue architecture maintenance. Mutation of any of its components results in loss of cell-cell adhesion, thereby contributing to neoplasia. E-cadherin/CDH1 gene germline mutations have been recognized in families with an inherited predisposition to diffuse type of malignancy. This review focus mainly on Helicobacter pylori infection involved in gastric carcinogenesis through mentioned various mechanisms, thereby necessitating its eradication.

Key Words: gastric cancer, epidemiology, H. pylori, oncogenes, tumor suppressor genes, microsatellite instability, apoptosis

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Epidemiology

Gastric cancer remains a significant worldwide health burden. Although the incidence and mortality rates of this malignancy not positioned in the cardia have been decreasing in the last decades, it still remains second only to lung cancer as a leading cause of cancer mortality worldwide.[1] On the other hand, adenocarcinoma of the cardia and gastroesophageal junction appears to have increased in the past two decades in both hospitalized and population-based studies from several geographic regions.[2]

Importantly, the remarkable decrease of adenocarcinoma of the stomach in the United States during the last 70 years has occurred primarily for the intestinal type of the disease, which is associated with *Helicobacter pylori (H. pylori)* infection (class I carcinogen, WHO), achlorhydria and intestinal metaplasia. The incidence of the diffuse-type gastric cancer has remained constant over time. In contrast, apart from the proximal gastric cancers, there has been a relative increase in distal esophageal adenocarcinomas, particularly those associated with Barrett's esophagus.[3,4]

These epidemiologic variables provoke intense efforts to identify new features in depth and strategies of molecular biology for better understanding the pathogenesis and/or management of gastric cancer.[4]

Classification – Etiology

According to Lauren classification, gastric cancer can be subdivided into two distinct pathologic entities, diffuse (infiltrating or scattered malignant cells or islands of cells) and intestinal (gland-forming or expansive) that have different epidemiologic and prognostic features.[5] Apart from the same frequency throughout the world, diffuse type gastric cancers present more diffusely in the stomach and earlier in life, arise without identifiable precursor lesions and tend to spread contiguously into the peritone-

um, whereas intestinal type gastric malignancies tend to spread hematogenously and are accompanied by a worse prognosis than the intestinal type. The intestinal type of malignancy is more closely linked to environmental and dietary risk factors and is the type of cancer that is now declining worldwide. The importance of distinguishing these two main histopathologic types of gastric cancer is highlighted by the finding of specific genetic changes associated with the different types.[4]

It is now thought that the development of the intestinal type of malignancy is possibly a multistep process, as has been well described in the pathogenesis of colon cancer. In particular, the progression from adenoma to colon carcinoma results from the accumulation of molecular genetic alterations involving mainly 3 factors: activation of oncogenes; inactivation of tumor suppressor genes; and abnormalities in genes involved in DNA mismatch repair.[6] The contention that the pathogenesis of the intestinal-type gastric cancer is also a multistep process, comprising gastric mucosal metaplasia-dysplasia-carcinoma sequence, is supported by the evidence that both atrophic gastritis and intestinal metaplasia are found in higher incidence in patients with intestinal-type cancer and in areas with high incidence of gastric cancer.[4,5] This multistep model of gastric cancer postulates that initially there is inflammation, caused by *H. pylori* infection, and by exposure of toxins (preserved foods, high salt diet, bile salts), which can lead to the development of chronic active gastritis. In a subset of these patients, this inflammatory process leads to the development of atrophic gastritis, followed by intestinal metaplasia, dysplasia and, ultimately, early and advanced gastric cancer. Unlike the case of colon cancer, the precise genes involved in each step of this progression are still not accurately defined. At present, it still remains tentative whether the diffuse type of gastric cancer follows an analogous histopathologic progression.[2]

Genetic factors

The accumulation of multiple genetic alterations leading to oncogene overexpression, tumor suppressor loss and defective DNA mismatch repair is associated with tumors of the gastrointestinal tract, including gastric cancer[6,7] (Table 1).

In particular, gastric carcinomas are believed to evolve from native gastric mucosa or intestinal metaplastic mucosa that undergoes genetic and epigenetic alterations involving either the suppressor pathway (defects in tumor suppressor genes) or the mutator pathway (defects in DNA mismatch repair genes).[8] Progress has been made in our understanding of the genetic changes that occur mostly in the intestinal type of gastric cancer. The most frequent genetic abnormalities found tend to be loss of heterozygosity (LOH) of previously described tumor suppressor genes. Of note, mutations that disrupt the biological function of these genes have been found in association with cancers of the stomach, as well as the esophagus and colon. The gene that has garnered the most attention is the tumor suppressor p53. Early studies reported that LOH (60-70%) and mutations (38-71%) of the p53 gene are quite frequent in gastric cancer. In addition, p53 mutations are also observed in intestinal metaplasia (38%) and gastric dysplasia (58%), suggesting that mutations of the p53 gene may be an early event and perhaps work together with ras oncogene in the pathogenesis of gastric cancer.[9] Further evidence for a role of p53 in the early stages of gastric cancer development comes from studies in mice that are hemizygous for p53, which display an increased proliferative response to *H. pylori* infection compared with wild-type mice. Increased proliferation is correlated with an increased risk of developing gastric malignancy. From another viewpoint, recent studies indicate that the inducible nitric oxide synthase (iNOS), vascular endothelial growth factor (VEGF) and the tumor suppressor p53 are fundamental play-markers of the angiogenic process. Overexpression of iNOS and VEGF has been shown to induce angiogenesis in tumors, whereas p53 suppresses angiogenesis by down-regulating VEGF and iNOS. On the other hand, mutations of the p53

Table 1. Oncogenes, tumor suppressor genes and DNA mismatch repair genes involved in gastrointestinal tract tumors

	Colon	Esophagus	Stomach
Oncogenes			
Ras	+		+
c-myc	+	+	+
c-erb B1			+
c-erb B2	+	+	+
hst-1	+		+
trk	+		
c-raf	+		
c-scr	+		
c-myb	+		+
c-yes			
c-mos			
c-fos			
Tumor Suppressor Genes			
p53	+	+	+
APC	+	+	+
DCC	+	+	+
MCC	+	+	+
DPC4	+		
DNA Mismatch Repair Genes			
hMSH2, hMLH1	+	+	+

gene have been thought to upregulate VEGF and possibly iNOS.[10] In this regard, *H pylori* infection induces p53 mutations,[11] up-regulation of VEGF expression[12,13] and iNOS expression and subsequent DNA damage as well as enhanced anti-apoptosis signal transduction,[14] thereby contributing to gastric carcinogenesis.

LOH at the 5q allelic locus, the site of the "Adenomatous Polyposis Coli" (APC) and "Mutated in Colon Cancer" (MCC) genes, occurs in over a third of gastric tumors but not in gastric dysplasia, with LOH being more common in the intestinal type regardless of stage.[2] APC gene abnormalities may lead to disruption of normal cell-cell adhesion through altered association with molecules called catenins and cell adhesion molecule E-cadherin, which is a transmembrane glucoprotein that binds catenins. The E-cadherin-catenin complex is an important element for maintaining intercellular adhesion and plays a critical role on the maintenance of normal tissue architecture.[15] Mutation of any of its components is believed to result in loss of cell-cell adhesion, thereby contributing to neoplasia, and is associated with poor differentiation and increased invasiveness of carcinomas.[6] Additional evidence supporting a role for APC in the pathogenesis of some forms of gastric cancer comes from the fact that Familial Adenomatous Polyposis patients have a tenfold higher risk of developing gastric cancer compared with the general population. Mutations of APC gene occur in up to 20% of sporadic gastric cancers and gastric adenomas, mainly in well-differentiated intestinal gastric cancers in which up to 60% may have APC mutations.[2] The mechanism of action of the APC gene is to sequester and inactivate cytoplasmic β-catenin preventing the formation of β-catenin/LEF (lymphoid enhancer factor), which acts as a growth-promoting transcription factor. It is important to note that, in intestinal-type gastric cancers β-catenin mRNA levels are greatly enhanced.[16] In this regard, *H pylori* infection induces disruption of E-cadherin/catenin–containing adherens junctions on gastric epithelium, leading to gastric oncogenesis.[17]

A number of other genes have been reported to be either mutated or suppressed in gastric cancer, although their relative significance in the pathogenesis of gastric cancer remains to be determined (Table 2).[2,18]

A variety of oncogenes and the proteins encoded by them also appear to play a significant role in the pathogenesis of gastric cancer. The best studied and most common oncogene alteration in colonic neoplasm involves the ras oncogene, which also works together with p53 gene mutation in gastric carcinogenesis[9] and upregulates the gene expression of gastrin. The latter is an oncogenic growth factor contributing to gastric and colon carcinogenesis.[6,19] Chronic hypergastrinemia in mice can synergize with *H. pylori* infection and contribute to eventual parietal cell loss and progression to gastric cancer.[20] The gastric cultured epithelial cells exhibit the expression of gastrin receptors, and gastrin shows antiapoptotic activity through the upregulation of Bcl-2 and survivin. Moreover, gastrin stimulates the gene and protein expression of cyclooxygenase (COX)-2 and hepatocyte growth factor (HGF) in human cultured gastric cancer cells, thereby contributing to tumorigenesis.[19] In this regard, *H. pylori* infection may contribute to gastric carcinogenesis via induction of gastrin and COX-2 that may account for the stimulation of tumor growth, angiogenesis and reduction in apoptosis.[19] Therefore, *H. pylori* positive patients developing gastric or colon cancer should be considered for *H. pylori* eradication to reduce the *H. pylori* provoked hypergastrinemia and COX-2 overexpression in the tumor tissue.

Table 2. Genetic changes in gastric adenocarcinoma

Changes	Gene	Frequency (%)
Suppression/Loss	p53	60-70
	FHIT	60
	APC	50
	DCC	50
	E-cadherin	<5
Amplification/Upregulation	COX-2	70
	HGF/SF	60
	VEGF	50
	c-Met	45
	AIB-1	40
	β-catenin	25
	K-sam	20
	ras	10-15
	c-erb B-2	5-7
Microsatellite instability (MSI)		25-40
DNA aneuploidy		60-75

Increased COX-2 expression was noticed in gastric carcinomas, Barrett's esophagus and esophageal adenocarcinomas, and colorectal adenomas and carcinomas.[21] COX-2 appears to be mutagenic and tumorigenic in vitro. Moreover, COX-2 overexpression may inhibit apoptosis and increases invasiveness of malignant cells.[21] CagA(+) *H. pylori* infection could upregulate the expression of COX-2 in gastric cancer in humans.[22] Furthermore, *H. pylori* infection might activate NF-κB, an oxidant-sensitive transcription regulator of inducible expression of inflammatory genes such as COX-2, which regulates human gastric cancer cell growth and proliferation. Thus, oxidant-sensitive transcription factor NF-κB may play a

novel role in the expression of COX-2 by *H. pylori* stimulation in gastric cancer cells.[23]

Besides, COX-2 overexpression enhances prostaglandin (PG) synthesis and the importance of prostaglandins (PGE_2) in the progression of a chronic inflammation or neoplasia has long been recognized. It is becoming clear that these compounds are implicated in cell proliferation and inhibition of immune surveillance; therefore, overproduction of PGs could favor malignant growth.[21] Specifically, synthetic machinery and receptors for PGE_2, prominently expressed by T lymphocytes in gastric mucosa at the boundary of normal mucosa with tumor cells, may play a central role in prostanoid-driven tumorigenesis of this tissue.[24] In addition, binding of HGF to its receptor (c-Met) regulates gastric cancer progression and metastasis, upregulates the expression of COX-2 gene and increases PG synthesis in gastric mucosa cells.[25]. Importantly, *H pylori*, apart from inducing COX-2 expression, also increases PGE(2) synthesis[26] and the increased levels of PGE2 in the presence of cagA+ infection could be an important factor by which cagA+ strains enhance the gastric mucus layer protective functions leading to established colonization, gastritis and increased risk of gastric cancer.[27] On the other hand, inhibition of COX-2 prevents growth of gastric cancer xenografts in nude mice, and aspirin use (which inhibits both COX-1 and COX-2) decreases the risk of developing gastric cancer.[2] Therefore, applying COX-2 selective (or nonselective) inhibitors reduces inflammation, suppresses carcinogenesis in the gastrointestinal tract and could be an effective and promising way to prevent *H. pylori*-related gastric cancer.[22,28]

The c-Met gene, a proto-oncogene member of the tyrosine kinase growth factor receptors, is amplified in 10.2% and overexpressed in 46.1% of gastric cancers. Its ligand, HGF/scatter factor (HGF/SF), is also overexpressed in 67% of gastric cancers.[2] *H. pylori* activates the c-Met, promoting gastric cancer.[29] Moreover, a higher frequency of c-Met expression is observed in α-fetoprotein (AFP)-producing gastric cancer and is associated with decreased apoptosis, high incidence of liver metastasis and poor prognosis. A higher expression of c-Met might be one explanation for the poorer prognosis of AFP-producing gastric cancers, because HGF and its receptor, c-Met, are known to induce mitosis and cell movement and to promote tumor progression.[30,31]

Amplification and/or overexpression of putative trophic factors have also been observed in gastric cancer. VEGF is a known angiogenic factor that promotes neovascularization of tumors, generally increasing the risk of invasion and metastases. It is worthy to note that, VEGF is overexpressed in up to 54% of gastric cancers and correlates with the depth of invasion, the staging of gastric carcinoma, an increased risk of lymph node and liver metastases, and with disease recurrence.[2,32] IL-6 may play a role in the angiogenesis of gastric carcinoma via modulation of VEGF. Furthermore, IL-8 (induced by *H pylori* infection) acts as an angiogenic factor for human gastric carcinomas, upregulates matrix metalloproteinase (MMP)-9 expression and increases invasive activity of gastric carcinoma cells. The chemokine IL-8 (CXCL8) appears to exert potent angiogenic properties on endothelial cells through interaction with its cognate receptors CXCR1 and CXCR2.[33]. IL-8 and VEGF (contributing to *H. pylori*-related gastric carcinogenesis)[12] may be independent and important prognostic factors in human gastric carcinomas.[34] Moreover, the expressions of iNOS and VEGF are closely related to tumor angiogenesis and are involved in the advancement and the lymph node metastases. Thus, it would appear that VEGF may play a role in the development of advanced gastric cancer, and therapy with VEGF antibodies may be a potent therapeutic strategy against human *H. pylori* -elated gastric cancer.[35]

Recently, Houghton et al.[36,37] showed that *H. pylori*-induced inflammation in mice caused the migration of stem cells originating from bone marrow to the stomach, where they subsequently developed gastric tumors. These stem cells progress through metaplasia and dysplasia to intraepithelial cancer, suggesting that epithelial cancers can originate from bone marrow-derived stem cells (BMDCs). In this regard, we recently conducted a pilot study (Kountouras et al. unpublished data) using tissue sections of biopsies of human gastric cancer in which *H. pylori* bacteria were detected by cresyl violet staining. Moreover, stem cells and neovessels were detected by immunohistochemical method using a monoclonal antibody anti-CD 34; CD 34 is a surface glycoprotein expressed on hematopoietic stem cells. In addition, cyclin D1, involved in the regulation of cell proliferation, was also detected by the immunohistochemical method. Therefore, it would be reasonable to speculate that chronic infection of C57BL/6 in mice and humans with *H. pylori* induces repopulation of the stomach with BMDCs that may facilitate gastric cancer progression. These findings present a new way of thinking about the pathogenesis of upper gastrointestinal malignancy and lead to the observation that BMDCs are the origin of *H pylori* –induced gastric cancer also combined with supporting observations of BMDCs in other tumors such as Barrett's esophageal adenocarcinoma, Kaposis sarcoma or benign and malignant tumors of skin.[37]

The data regarding the genetics of diffuse gastric can-

cer are less complete. Mutations in the E-cadherin gene have been associated with the development of the diffuse type of gastric cancer.[2,38] In particular, germline mutations in the E-cadherin/CDH1 gene have been recognized in families with an autosomal-dominant inherited predisposition to gastric cancer of the diffuse type.[3,39] The cumulative lifetime risk of developing gastric malignancy in CDH1 mutation carriers is greater that 70%, and women of these families also have an increased risk for developing breast cancer.

Further evidence supporting the role for E-cadherin in gastric oncogenesis comes from studies showing that suppression of E-cadherin occurs in 51% of cancers, with a higher percentage found in the diffuse type of cancers. E-cadherin methylation is an early event in gastric carcinogenesis and is initiated by *H. pylori* infection.[40] Furthermore, E-cadherin underexpression is associated with increased rate of lymph node metastases and decreased survival. In this respect, gastric adenocarcinoma in young patients has a poor prognosis, possesses aggressive histopathological features, exhibits reduced expression of E-cadherin and β-catenin and demonstrates lower microsatellite instability (MSI) than tumors in older patients.[41]

IL-1 gene cluster polymorphisms are associated with an increased risk of both hypochlorhydria induced by *H. pylori* and gastric cancer.[42] Polymorphisms in IL-1-β and its endogenous receptor antagonist are associated with risk of *H. pylori*-related gastric cancer.[43] Also, IL-1-β polymorphisms are associated with increased risk of gastric cancer not only in whites, but also in patients from the Far East (Japan).[44] From another viewpoint, *H. pylori* infected patients exhibit overexpression mainly of ki-67 and also of both bcl-2 and bax proteins in the upper gastrointestinal tract mucosa, thereby, indicating increased proliferation leading to gastric oncogenesis.[45] These last findings, as well as all previously mentioned data on the various mechanisms by which *H. pylori* is involved in gastric carcinogenesis, emphasize the need for *H. pylori* eradication in coping with gastric cancer.

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