Phenotypic and Genotypic Events in Gastric Carcinogenesis

Pelayo Correa and Yih-horng Shiao
Department of Pathology, Louisiana State University Medical Center, New Orleans, Louisiana

Abstract

Two main histological variants of gastric carcinoma have been identified: intestinal and diffuse types. The former is preceded by a sequential chain of events characterized as chronic gastritis, atrophy, intestinal metaplasia, dysplasia, intramucosal carcinoma, and invasive neoplasia. The second type (diffuse) lacks well-recognized precursor changes. Genotypic events in the gastric precancerous process are described, but a clear model of their sequence and relevance is lacking. Cadherins may play a role in determining which type of carcinoma develops. Translocated promoter region-MET rearrangements have been identified since early stages of the process. p53 alterations are reported beginning with the dysplasia stage utilizing immunohistochemical techniques. Single-strand conformation polymorphism and sequencing analysis show alterations in early stages, especially G:C to A:T transitions.

Phenotypic Events

Gastric carcinoma in humans is characterized by 2 histopathological patterns which have demonstrated value in terms of epidemiological parameters of demographic distribution and survival. The 2 types also differ drastically in the phenotypic characteristics of the precursor stage. The most common variant in populations at high cancer risk is the so-called intestinal type in which the malignant cells are united to each other so as to form glandular structures which somewhat resemble the glands of the gastrointestinal tract. The overriding etiological factors in this type are of an environmental nature and related to diet and infection. This type is preceded by a long chain of events identifiable with the usual stains such as hematoxylin-eosin. The main stages of the process have been characterized as chronic gastritis, atrophy, metaplasia of the small intestinal and colonic types, dysplasia, intramucosal (“early”) carcinoma, and invasion. A hypothesis has been proposed linking specific stages with specific etiological agents. Of particular interest is the abnormal expression of sulfomucins and Lewis antigens, which when occurring simultaneously increase the relative risk of dysplasia more than 10-fold.

In populations at low risk the second histological type, namely, the diffuse carcinoma, is relatively more frequent. In this type the neoplastic cells are independent of each other and invade the organ without forming well-defined structures such as glands. No clear precancerous lesions have been identified for this variant. The role of environmental factors for this type appears less important than the genetic influences.

Genotypic Events

Contrary to the situation for phenotypic abnormalities, the existing data concerning genotypic abnormalities are confusing. A considerable number of them has been described, and several recent literature reviews are available. No clear picture has emerged to indicate which abnormalities are pathognomonic for gastric carcinoma, at which stage of the process they appear, and what interpretation should be given to the rather disparate findings of the published series. Fig. 1 illustrates some findings that suggest the appearance of molecular lesions at specific points in the chain of causation of the intestinal type of carcinoma. In the case of ras abnormalities, the reports differ substantially regarding the frequency and type of alteration, but a consensus appears to be developing that K-ras is associated with intestinal metaplasia and represents intestinal phenotypes in gastric carcinomas. There have been reports of molecular lesions similar to those seen frequently in intestinal carcinomas, especially involving the APC and the DCC genes. We have studied the p53 and the TPR-MET abnormalities in gastric cancer and precancerous lesions.

In cooperation with investigators from the University of Padova, immunohistochemical stains utilizing polyclonal antibodies (CM-1) against p53 protein were applied to 33 specimens in which areas of carcinoma and dysplasia were identified and examined independently. The stains were positive in 61% of gastric carcinomas, 64% of severe dysplasias, 27% of moderate dysplasias, and 19% of mild dysplasias. In the same series gastric mucosa without metaplasia or dysplasia was consistently negative. This abnormality, therefore, appears specifically at the stage of dysplasia and increases in prevalence as the precancerous process becomes more advanced. It would appear that the frequency of this abnormality continues to increase after the stage of invasive carcinoma is reached because Martin et al. (11) have shown that the prevalence is higher in poorly differentiated than in better differentiated tumors. Polymorphonuclear leukocytes, known sources of oxidative species capable of inducing molecular alterations in the DNA molecule, are frequently observed in the immediate vicinity of metaplastic, dysplastic, and neoplastic gastric epithelial cells. In 12 cases, gastrectomy specimens were available that contained the full spectrum of precancerous lesions. They were stained with anti-p53 antibodies, and tissues were processed with polymerase chain reaction, single-strand conformation polymorphism analysis, and DNA-sequencing techniques. Table 1 shows the results of the analysis. Alterations of the p53 gene were found in 9 cases. In 3 cases, DNA base substitutions without a change of amino acid were detected throughout all of the precancerous stages and carcinoma. Deletions and missense mutations were found only in exon 5 and exon 7. Cases with missense mutations in this region also showed positive immunohistochemical stain. Five of 9 mutations were G:C to A:T transitions. The type of mutation has been frequently reported in gastric carcinomas as reported in Table 2 (12–17). Mutations of C to T have been reported to be induced by nitric oxide (18, 19). Our preliminary results suggest that p53 alterations occur in the carcinogenesis process before they can be detected with immunohistochemical techniques and may be linked to nitric oxide or similar carcinogens, which can originate in polymorphonuclear leukocytes in intimate contact with dividing cells.

Abnormalities involving the TPR-MET rearrangement have been investigated in collaboration with Massachusetts Institute of Technology investigators. The TPR-MET rearrangement was originally reported in an in vitro transformed cell line of human osteosarcoma exposed to N-methyl-N-nitro-N-nitrosoguanidine, a strong gastric carcinogen in experimental animals. It involved fusion of the TPR on chromosome 1 to the 5' region of MET gene on chromosome 7. Our preliminary results suggest that p53 alterations occur in the carcinogenesis process before they can be detected with immunohistochemical techniques and may be linked to nitric oxide or similar carcinogens, which can originate in polymorphonuclear leukocytes in intimate contact with dividing cells.

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2 The abbreviations used are: TPR, translocated promoter region.
appears that this is a very early event in the process which ultimately may lead to gastric cancer. The main cause of superficial gastritis is infection with *Helicobacter pylori*.

In the case of diffuse carcinomas, the absence of a well-recognized series of precancerous events does not allow speculations concerning molecular alterations which may lead to malignant transformation. Recent developments in the expression of calcium-dependent cell adhesion molecules (called cadherins) may advance our understanding of the process. These transmembrane glycoproteins are localized in the lateral borders of the epithelial cells and are responsible for intercellular binding. They have been found to be absent or functionally defective in diffuse gastric carcinomas (23, 24). Some gastric cancer cell lines, *i.e.*, MKN 28, maintain strong expression of E-cadherin in the cell-cell adhesion sites and originated in well-differentiated (intestinal type) adenocarcinomas. Other cell lines, *i.e.*, TMK-1 reveal weak E-cadherin expression and originated in poorly differentiated (diffuse) scirrhous adenocarcinomas. According to Tahara (4), this finding may be relevant to the natural history of the 2 types of gastric carcinoma: “stromal fibroblasts stimulated by tumor-derived growth factors or cytokines may secrete hepatocyte growth factor in a paracrine manner which can bind to c-met protein on tumor cells.” In the presence of E-cadherin the proliferating tumor cells would form glands, and in its absence the tumor cells would proliferate and invade the surrounding tissues independently of each other. In this way the target cell may respond differently to similar carcinogenic insults.

### References

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**INTESTINAL-TYPE GASTRIC CARCINOMA**

- Normal
- Superficial Gastritis
- Atrophic Gastritis
- Intestinal Metaplasia
- K-ras
- Dysplasia
- Carcinoma
- C-erb-2

Fig. 1. Intestinal type gastric carcinoma.
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