Phenotypic and Genotypic Events in Gastric Carcinogenesis

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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.

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.

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. It developed fusion of the TPR on chromosome 1 to the 5′ region of MET gene on chromosome 7. This abnormality has been linked to spatial arrangement of cells in the formation of glandular lumens. In our material, TPR-MET rearrangement has been found not only in gastric carcinomas but in all of the precursor stages, including the earliest stage identifiable with morphological techniques, namely, superficial gastritis. It then

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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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