Genetic Instability in Pancreatic Cancer and Poorly Differentiated Type of Gastric Cancer

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Abstract

To examine genetic instability during carcinogenesis, we screened 171 carcinomas of the breast, liver, proximal colon, stomach, pancreas, uterine cervix, and ovary for replication error at four microsatellite marker loci on chromosomes 2, 3, and 17. A significantly high incidence of genetic instability was observed in pancreatic (6 of 9 tumors) and gastric cancers (22 of 57 cases). In other types of carcinoma, the incidence of replication error-positive cases was relatively low (3-16%). Among gastric carcinomas, significantly more replication error-positive cases were observed in the poorly differentiated types (16 of 25 cases) than in well differentiated ones (22 of 57 cases). In other types of carcinoma, the incidence of replication error-positive cases was relatively low (3-16%). Among gastric carcinomas, significantly more replication error-positive cases were observed in the poorly differentiated types (16 of 25 cases) than in well differentiated types (15 of 25 cases) (P = 0.0023 by Fisher's exact test). Our results suggested that genetic instability is likely to play an important role in development of pancreatic and gastric cancers, particularly poorly differentiated adenocarcinomas.

Introduction

Genetic alterations in simple repeated sequences constitute a newly recognized class of human mutations causing disease (1-3). These regions are genetically unstable and susceptible to RERs (1, 4, 5) as judged by their unusually high mutation rates in vivo (6) and in vitro (7) and by their highly polymorphic nature in the human population. During studies of HNPCC, Aaltonen et al. (8) found evidence that genetic instability, probably due to error during replication/repair by strand misalignment, correlated with tumorigenesis in colorectal and other carcinomas that developed in affected members of HNPCC families. Linkage analyses suggested that a variant allele triggering this instability might be located on the short arm of chromosome 2 (9). The concept that multiple genetic alterations affecting protooncogenes and tumor suppressor genes are involved in development of various human cancers is now widely accepted. However, still unclear is whether genetic instability caused by failure of replication fidelity occurs in tumors in a particular organ or in many organs. On the basis of the observations cited above, it would be of great interest to know whether the genetic instability observed in HNPCC-related tumors also occurs in sporadic tumors in other organs. In this study, we compared the sizes of microsatellite loci between tumor DNAs and their corresponding normal DNAs in sporadic tumors of the breast, liver, stomach, proximal colon, pancreas, uterus, and ovary. We found frequent genetic instability in pancreatic carcinomas and in poorly differentiated gastric carcinomas.

Materials and Methods

Tumor DNAs and corresponding normal DNAs were obtained from 171 patients as described previously (10, 18). The tumors included 26 breast cancers, 29 hepatocellular carcinomas, 18 proximal colon cancers (12 in ascending colon, 6 in caecum), 9 pancreatic cancers, 13 cervical cancers, 19 ovarian cancers, and 57 gastric cancers. Gastric cancers were further classified into three histopathological types according to WHO criteria (11); 18 were well differentiated, 8 moderately differentiated, and 7 poorly differentiated adenocarcinomas.

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2 The abbreviations used are: RER, replication error; HNPCC, hereditary non-polyposis colorectal cancer; PCR, polymerase chain reaction; RER(+), RER positive.
patients studied here were not available to us, the tumors revealing RER(+) might reflect inherited susceptibility to genetic instability. An altered replication factor causing instability of the genome could influence to expression of genes which are important for controlling the normal proliferation of cells.

To further characterize genetic instability in the 57 gastric carcinomas, we divided this group of tumors into three histological types (Table 2). It is notable that the frequency of RER was significantly higher in poorly differentiated tumors than in the well differentiated type \( P = 0.0023 \) by Fisher’s exact test or the signet-ring cell type \( P = 0.012 \). The incidence of RER in poorly differentiated gastric carcinomas was also significantly high in comparison with that in breast \( P = 0.000004 \), liver \( P = 0.000001 \), proximal colon \( P = 0.0006 \), uterine cervix \( P = 0.005 \), or ovary \( P = 0.002 \).

Among the 25 poorly differentiated adenocarcinomas of the stomach which were examined at the only two loci, eight were RER(+) at both the loci. Three of the 9 pancreatic carcinomas were also RER(+) at the 2 or more loci. These results support the genomic instability in these type of tumors.

Our data clearly imply that genetic instability plays an important role in development of pancreatic cancer and of gastric cancer, particularly in the poorly differentiated type. Genetic alterations previously reported in gastric carcinomas have included amplifications of the erbB-2 and K-sam genes and point/frame-shift mutations of the K-ras, p53, and APC genes; however, the genetic alterations are observed relatively infrequently except in the case of APC (16, 18). Among these mentioned, only amplification of the K-sam gene seems to be specific to the poorly differentiated type of gastric cancer (17).

The microsatellite instability reported here is the most frequent genetic alteration thus far detected in poorly differentiated gastric carcinomas. It appears to be specific to this type of gastric cancer; in contrast, somatic mutations of the APC gene are frequent in well differentiated gastric carcinomas but very rare in the poorly differentiated type (18). Previously, we had examined gastric cancers for somatic mutations in part of the APC gene, which is responsible for familial adenomatous polyposis and appears to be one of the tumor suppressor genes associated with development of sporadic colorectal carcinomas (19). In those studies, we found somatic mutations in 20–40% of well differentiated gastric cancers but detected none in 19 poorly differentiated tumors. The data presented here further support our previous hypothesis that pathologically distinct subtypes of gastric carcinomas undergo different genetic pathways during tumorigenesis. Furthermore, generally earlier onset of poorly differentiated gastric cancers (55 years old) compared to well differentiated types (65 years old) may imply the presence of a genetic factor associated with susceptibility to genetic instability in patients who develop the poorly differentiated type of gastric carcinoma.

We have shown that the genetic instability of loci containing dinucleotide repeats is magnified in some pancreatic cancers and gastric cancers of poorly differentiated type. If the mechanism for this instability and the stage at which it occurs during development/progression of carcinogenesis in these cancers could be defined more clearly, a test for alteration in microsatellite loci might provide useful prognostic information and contribute to an understanding of the biological significance of such myotonus.

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