

K-ras as a Genetic Marker in Pancreatic Cancer

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INTRODUCTION

Molecular biochemical techniques have demonstrated that cancer is a genetic disease, and the application of these techniques has been proposed for the screening of gastrointestinal malignancies (1). Transforming ras oncogenes are frequently identified in human carcinoma. Point mutations of K-ras result in the expression of altered protein products that are capable of transforming cells into malignant phenotypes (2,3,4). K-ras mutations have been detected in a variety of human neoplasms at variable frequencies.

Most patients with pancreatic cancer are already advanced at diagnosis. Pancreatic tumors are accurately diagnosed using various imaging tests, but the difficulty in detecting early pancreatic cancer contributes to the high mortality from the disease. The most common sites of extralymphatic involvement are the liver and peritoneum. The pancreas can also be the site of metastasis from breast cancer, lung cancer, and cutaneous melanoma (5). Pancreatic adenocarcinoma is characterized by the presence of K-ras mutations at a high frequency.

K-RAS GENE

The role of the ras gene in human cancer was first identified in 1981 (6). Some human cancer cells were shown to contain DNA sequences capable of inducing neoplastic transformation. Three highly related ras genes have been identified in human: H-ras, K-ras and N-ras (7,8,9). Each encodes a guanine nucleotide-binding protein with a molecular weight of 21000. Biochemical and genetic data have implicated Ras proteins in the transduction of growth and the differentiation signals from activated receptors to downstream protein kinases (3,10). Oncogenic mutations in ras genes appear to reduce the ability of ras to hydrolyze guanosine triphosphate (GTP) to guanosine diphosphate. Mutant ras remains in the GTP-bound or active state, and the normal signal transduction process is altered (11,12). Mutations of the ras gene have been identified in 75%-90% of pancreatic adenocarcinomas, 50% of colorectal carcinomas, and 25% of acute nonlymphocytic leukemias(2).

PANCREATIC CANCER

For the majority of patients, adenocarcinoma of the pancreas remains a highly lethal disease regardless of treatment modality. An estimated 28,000 new cases of pancreatic cancer occur each year in the United States.

More than 25,000 deaths per year are attributed to the disease, making it the fourth leading cause of cancer-related death. The prognosis is bleak, with an overall 5-year survival rate of between 2% and 3%. Almost all patients die of their disease within 2 years of diagnosis (13,14). Given the poor response to conventional treatment and dismal prognosis of the disease, patients and clinicians are willing to explore new therapies. Surgical resection provides the only meaningful chance for cure and increased survival in patients with pancreatic carcinoma. Only 17% of all patients admitted with adenocarcinoma of the pancreas undergo resection (15).

DIAGNOSIS OF PANCREATIC CANCER

Pancreatic cancer is accurately diagnosed using common imaging tests, but these tests do not reliably detect the disease at its early stages. On the other hand, the combined use of abdominal ultrasonography and endoscopic retrograde cholangiopancreatography (ERCP) can detect 90% of patients with pancreatic cancer, including these at the earliest stages (16). Computed tomography (CT) is more accurate than ultrasonography (17).

To complement imaging methods and simplify the diagnosis of pancreatic cancer, investigators have developed serum markers that may be hallmarks of neoplastic transformation. But, all serum tumor markers lack tumor sensitivity and specificity, making them unreliable for the diagnosis of pancreatic cancer. The sensitivities of CA 19-9 and CEA are 71% and 62%, respectively (18).

Fine-needle aspiration biopsy of the pancreas, one of the major advances in the diagnosis of pancreatic tumors, has been confirmed to be a reliable procedure (19,20). However, several authors suggest that the use of preoperative fine-needle aspiration results in peritoneal contamination by tumor cells and increases the risk for intraperitoneal tumor dissemination (21,22). More recently, laparoscopy has been suggested as a sensitive method for detecting metastatic disease in pancreatic cancer patients (23).

It is unknown if gene mutations can be used to detect early pancreatic cancer. The most common gene abnormality in pancreatic cancer is a K-ras mutation. Up to 90% of pancreatic adenocarcinomas harbor activated K-ras genes mutations (24,25,26). Fifty to 70% of pancreatic cancers have mutations of the p53 tumor suppressor gene (27,28), and 50% have reduced expression of the DCC gene (29,30).

PROGNOSTIC MARKERS IN PANCREATIC CANCER

Researchers examined several prognostic factors to determine their impact on survival in pancreas cancer patients. Lymph node metastasis, tumor size, and poor tumor

differentiation are commonly considered to have significant effects on longterm survival (31). However, few studies have identified significant increases in mortality in association with the presence of K-ras mutations (25).

K-RAS MUTATIONS IN CHRONIC PANCREATITIS

It is generally believed that detection of a K-ras mutation can sufficiently discriminate pancreatic carcinoma from a normal pancreas. This suggests that K-ras offers promise as a sensitive marker for the presence of a pancreatic cancer. However, we know that the presence of a K-ras mutation does not always coincide with the presence of cancer cells, since K-ras mutations have been detected in pancreatic duct hyperplasia in patients with chronic pancreatitis (32). Patients with chronic pancreatitis are also at increased risk for developing pancreatic cancer, having a cumulative risk of 1.8% at 10 years and 4% at 20 years (33). K-ras mutations were also identified in an animal model of hyperplastic lesions, and conversion from hyperplasia of the duct cell into pancreatic cancer has been shown in this model (34). Pancreatic ductal mucinous cell hyperplasia is neoplastic and might represent the early precursor lesions of pancreatic adenocarcinoma. Further investigations are necessary to clarify and confirm the molecular features of these findings.

K-RAS MUTATIONS IN SECONDARY SOURCES

Biological phenomena have been used as the basis of a diagnostic test for various cancers. The detection of K-ras mutations in secondary sources may form the basis for the development of new approaches to detect pancreatic cancer earlier and less invasively, as well as to differentiate it from benign conditions of the pancreas. The high prevalence of K-ras mutations in pancreatic cancer suggests that this gene offers promise as a sensitive molecular marker for the presence of carcinomas.

K-ras mutations in patients with pancreatic cancer have been identified in many materials obtained from a variety of sources. Stool, blood, duodenal contents, pancreatic juice, fine needle aspirates, and pancreatic duct brushings could be screened for the presence of exfoliated pancreatic cells containing point mutations in the K-ras oncogene (35,36,37).

FALSE NEGATIVE MUTATIONS IN SECONDARY SOURCES

Ductal tumor of the exocrine pancreas is the most common (90%) and well-studied pancreatic tumor type. On the other hand, K-ras mutations of nonductal exocrine or endocrine tumors are rarely involved in the genesis or progression (27).

Metastasis from the primary tumor is desirable, but the phenotype of the metastasis is not always the same as that of the primary tumor, since the tumors are heterogeneous or multicentric³⁸).

CONCLUSION

Cellular oncogenes play a role in the development of malignancies. Among cancer patients, the highest

frequencies of K-ras mutations occur in pancreatic adenocarcinomas. K-ras mutations are an early event and are preserved throughout the natural history of tumor progression.

K-ras mutation status does not predict stage at presentation or survival in patients undergoing surgical exploration for adenocarcinoma of the pancreas. If K-ras gene mutations prove to be specific to neoplastic and preneoplastic lesions of the pancreas, they may indeed be a powerful marker.

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