Oncogenes and tumor suppressor genes in pancreatic cancer

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Abstract: Recent advances in molecular biology have revealed that a number of oncogenes (K-ras, erbB-2, and Met) and tumor suppressor genes (p53, p16, APC, and DCC) contribute to the development of pancreatic cancer. This paper reviewed the present knowledge of oncogenes and tumor suppressor genes relevant to pancreatic cancer. Further studies on molecular alterations in pancreatic cancer may lead to a better understanding of tumor biology, offering a possibility of development of new diagnostic and therapeutic approaches in the future.

Key Word: Pancreatic cancer, oncogene, tumor suppressor gene, genetic mutation

Introduction

Pancreatic cancer is an important cause of deaths from cancers in the developed countries including Japan. It has remained to elucidate its biological characteristics and also to establish the method for its early detection. Recent advances in molecular biology has revealed that a number of oncogenes and tumor suppressor genes contribute to the development of pancreatic cancer. Improvement in its prognosis may be enabled by early molecular diagnosis and gene-targeting treatment in the future. This paper reviews the present knowledge of oncogenes and tumor suppressor genes relevant to pancreatic cancer.

K-ras

Ras gene family consists of three kinds of genes: N-ras, H-ras, and K-ras. Each of the genes encode a 21-kDa protein with GTPase involved in cell growth and differentiation. If K-ras was mutated, the protein seems to lose GTPase activity and thereby to affect the tumorigenic process by altering the signal transduction pathway across the membrane. K-ras point mutation at codon 12 has been detected in 80-90% of pancreatic ductal adenocarcinoma.
In the model of colorectal carcinoma, ras mutations are considered to be associated with progression of the neoplastic process, because 10% of adenomas <1.0 cm in size have as compared with 50% of adenomas >1.0 cm in size have ras mutations. In pancreatic cancer, K-ras mutation is not related to clinical course, metastasis, or prognosis. K-ras point mutation is known to be often detected in the ductal cell hyperplasias adjacent to pancreatic cancer. It is controversial whether these lesions are precancerous. In animal models, weekly injection of nitrosamine induced K-ras mutations in 28% of hyperplastic lesions, 48% of papillary hyperplastic lesions, 78% of carcinomas-in-situ, and 80% of invasive cancers of the pancreas. These results suggested that K-ras mutation is an early event in the multi-step progression to pancreatic neoplasm.

K-ras mutations in pure pancreatic juice (PPJ) have been identified in attempts to diagnose pancreatic cancer in early stage. Some investigators reported that K-ras mutation in PPJ preceded the definitive diagnosis of pancreatic cancer. We also experienced a case of small pancreatic cancer diagnosed by serial follow-up studies promptly by a positive K-ras point mutation in PPJ. However, K-ras mutation in PPJ was reported to be detected in 37-44% of patients with chronic pancreatitis, and long-term follow-up of patients with chronic pancreatitis revealed that no pancreatic cancer developed in mutation-positive patients. Further studies are needed to explore the clinical implication of detection of K-ras mutations in the early diagnosis of pancreatic cancer.

**erbB-2**

The erbB-2 (Her-2/neu) oncogene encodes a transmembrane protein with homology to the epidermal growth factor receptor. The erbB-2 protein is overexpressed in 25-58% of pancreatic cancers. Frequency of erbB-2 protein overexpression depends on tumor differentiation. Lower expression of erbB-2 was observed in poorly differentiated adenocarcinoma than in moderate or well-differentiated adenocarcinoma. As the erbB-2 protein is also overexpressed in mucinous hyperplasia of the pancreatic duct, the erbB-2 is suggested to be a potential mediator of growth factor-related signal transduction in pancreatic duct. Overexpression of erbB-2 was reported to be inversely related to the survival of patients with pancreatic cancer.

The positive rate of serum c-erbB-2 protein was reported as from 25% to 35%. Although reported that serum c-erbB-2 correlated with metastases and decreased survival rate in patients with pancreatic cancer, liver function influenced its serum levels.

**Met**

The c-Met oncogene encodes MET protein which is the receptor for hepatocyte growth factor (HGF). Although MET immunoreactivity was mild in acinar, ductal, and islet cells of the normal pancreas, it was intense in many of the duct-like cancer cell of human pancreatic adenocarcinoma. Since concomitant overexpression of HGF was observed in the pancreatic cancer, HGF is suggested to play a role in proliferation of pancreatic cancer as the autocrine or paracrine. MET immunoreactivity leads to a significantly longer survival than negative/focal staining. These data suggest that Met might have an important pathogenetic role during the early stages of development of pancreatic cancer.

**p53**

The p53 gene, which is localized on the short arm of chromosome 17, encodes p53 protein. The p53 protein is believed to play a prominent role in the regulation of cell cycles. After the identification of the p53, early observation suggested that p53 might function as an oncogene, because overexpression of p53 appeared to cause oncogenic transformation of cells. Several later studies, however, defined the normal function of the p53 to be anti-oncogenic because p53-null mice developed tumors much more. The p53 gene is inactivated in diverse human cancers by allelic deletions, point mutations that result from amino-acid
substitutions, and rearrangement\textsuperscript{31,32}. p53 gene mutations are observed in almost half of pancreatic adenocarcinomas\textsuperscript{3}.

Relationship between p53 mutations and survival in pancreatic carcinoma is controversial\textsuperscript{3}. Redston et al.\textsuperscript{33} found that there was no significant difference in overall survival between patients with and those without p53 mutations. In contrast, Nakamori et al.\textsuperscript{34} found that the median survival (6.2 months) of the patients with p53 mutations was significantly shorter than that (15.0 months) of those without p53 mutations.

Immunohistochemical examination for p53 protein was known to be useful to detect p53 gene mutation, because mutated p53 protein had a considerably longer half-life than wild p53 protein. Further studies have revealed that p53 protein accumulation is not always dependent on p53 gene mutation\textsuperscript{35}. Bourdon et al. reported that stabilization of the p53 protein depended also on mechanisms other than p53 gene mutation, such as binding other molecules of cellular origin\textsuperscript{35}. In addition, Maacke et al.\textsuperscript{36} reported that p53 protein overexpression in cytological specimens of PPJ samples was found in 59% of patients with pancreatitis and 67% of patients with pancreatic cancer: Overrepressed p53 in pancreatitis appears to be wild-type p53 and may result from DNA damage occurring during chronic inflammation.

\textbf{p16/CDKN2(MTS1)}

The p16 in the chromosome 9p21 encodes a protein which inhibits the activity of the cyclin-dependent kinase 4 (cdk4)\textsuperscript{37}. p16 is called multiple tumor suppressor 1 (MTS1) because inactivation of p16 was observed in many cancers\textsuperscript{38}. In pancreatic cancer, Caldas et al.\textsuperscript{39} reported that p16 was deleted homozygously in 15 (41%) and mutated in 14 (38%) of 37 pancreatic carcinomas.

The p16 gene mutations were reported to be more frequent in culture cell line than in primary tumors\textsuperscript{40,41}. The effect of p16 mutations on survival in pancreatic cancer has not been reported yet.

\textbf{APC}

APC, located on the chromosome 5q21, is the causative gene of non-polipotic familial adenoma of the colon. APC is known to participate in the early stage of multi-step carcinogenesis of the colon cancer\textsuperscript{42}. This gene was found to encode for a cytoplasmic protein with sequence homology to intermediate filament proteins such as myosin and keratin\textsuperscript{43}. Although Horii et al.\textsuperscript{44} found that APC mutations was observed in 40% of pancreatic cancer, another two studies\textsuperscript{45,46} showed frequencies below 3% of APC mutations was below 3%. Further studies are needed on APC gene in pancreatic cancer.

\textbf{DCC}

Approximately 70% of colon cancers have deletions in the region of 18q21, which was later found to be the locus of DCC (deleted in colorectal carcinoma gene)\textsuperscript{42}. Hohne et al.\textsuperscript{47} reported that 63.2% of pancreatic cancers had DCC mutations. They found that DCC mutations occurred more commonly in poorly differentiated pancreatic cancer\textsuperscript{47}.

\textbf{Conclusion}

Further studies on molecular alteration in pancreatic cancer may lead to a better understanding of tumor biology, offering a possibility of developing new diagnostic and therapeutic approaches in the future.

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