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## **Emerging Molecular Biology of Pancreatic Cancer**

**Ralph H. Hruban, MD**, Richard Schulick, MD, PhD, Daniel Laheru, MD,  
Joseph Herman, MD, MSc, Michael Goggins, MBBS

Departments of Pathology, Oncology, Surgery, and Radiation Oncology

The Sol Goldman Pancreatic Cancer Research Center

Johns Hopkins Medical Institutions

Baltimore, Maryland, USA

Infiltrating ductal adenocarcinoma, referred to here as “pancreatic cancer,” is fundamentally a genetic disease – a disease caused by inherited (germline) and acquired (somatic) mutations in specific genes. Many of the genes targeted in pancreatic cancer are now known, and the time is ripe to apply our knowledge of the molecular biology of pancreatic cancer to better patient care.

### **Genes Targeted in Pancreatic Cancer**

The genes somatically targeted in pancreatic cancer are summarized in Tables 1-3. Briefly, the tumor suppressor genes (Table 1) most frequently inactivated in pancreatic cancer include the *p16/CDKN2A* gene on chromosome 9p (90% to 95% of the cancers), the *TP53* gene on 17p (50% to 75%), and the *MADH4/DPC4* gene on 18q (55%). These genes are inactivated by a number of mechanisms including homozygous deletion, intragenic mutations coupled with loss of the second allele, and promoter hypermethylation. As shown in Table 2, the oncogenes most frequently activated in pancreatic cancer include the *KRAS2* gene on chromosome 12p (90%), the *BRAF* gene on chromosome 7q (5%), and the *AKT2* gene on chromosome 19q (10% to 20%). These are activated by point mutations and by amplification of the gene. DNA repair genes are also targeted in pancreatic cancer (Table 3), and these include the *BRCA2*, *FANC-C*, *FANC-G* and *MLH1* genes.

### **Genes Responsible for Familial Pancreatic Cancer**

Ten percent of pancreatic cancers have a familial basis, and, as listed in Table 4, some of the genes responsible for the aggregation of pancreatic cancer are known. These include the *BRCA2* gene (the second breast-ovarian cancer gene), the *p16/CDKN2A* gene (responsible for the familial atypical multiple mole melanoma [FAMMM] syndrome), the *PRSS1* gene (one of the familial pancreatitis genes), and *LKB1* (the Peutz-Jeghers syndrome gene). Three things stand out in these genetic syndromes: First, the risk of developing pancreatic cancer can be quantified in individuals with a mutation. Second, most of these germline genetic changes are associated with an increased risk of extrapancreatic malignancies as well. Third, some of these germline genetic changes are more common in certain groups. For example, a founder germline *BRCA2* gene mutation, the 6174 delT mutation, is present in ~1% of the Ashkenazi Jewish population.

These known genes only explain 10% to 20% of the familial aggregation of pancreatic cancer. We have established a registry for patients with a family history of pancreatic cancer to help facilitate the discovery of additional familial pancreatic cancer genes.

Patients and family members potentially interested in enrolling can contact:

Emily Palmisano, Coordinator, The National Familial Pancreas Tumor Registry, Johns Hopkins School of Medicine, 1550 Orleans Street, CRBII 341, Baltimore, MD 21231. Phone: 410-955-3502; E-mail: pancreas@jhmi.edu.

### **Genes Targeted in Other Pancreatic Neoplasms**

The  *$\beta$ -catenin* gene is activated in almost all solid-pseudopapillary neoplasms; the *PIK3CA* gene is activated in colloid carcinomas and the intraductal papillary mucinous neoplasms from which they arise; there is loss of a highly imprinted region of chromosome 11p in most pancreatoblastomas; and *KRAS2* gene mutations are extremely rare in acinar cell carcinomas. This correlation between tumor morphology and genetic changes led to the recognition of a new variant of ductal adenocarcinoma of the pancreas. Pancreatic cancers with microsatellite instability (MSI high) often have a distinct medullary histology.

### **Clinical Applications of the Genetic Changes in Pancreatic Cancer**

First, as noted in the discussion of the genes targeted in families, inherited genetic alterations can be used to quantify a person's pancreatic cancer risk. Patients at high risk will be the first to benefit from recently emerging tools to detect early pancreatic cancer and even the noninvasive precursors from which they arise. These inherited genetic alterations can also be used to quantify a person's risk of developing an extrapancreatic malignancy. For example, germline *p16/CDKN2A* mutations also increase the risk of developing melanoma, and regular skin examinations of germline *p16/CDKN2A* mutation carriers can save lives.

Second, gene-specific therapies specifically targeting a mutation present in a patient's cancer are emerging. Poly (ADP-ribose) polymerase (PARP) inhibitors may be particularly effective in treating pancreatic cancers with *BRCA2* gene mutations, and it has been suggested that l-alanosine and other inhibitors of the salvage pathway of AMP synthesis may be particularly effective in treating pancreatic cancers harboring homozygous *p16/CDKN2A* deletions that include the *MTAP* gene. Medullary cancers of the pancreas often show MSI and, based on findings in colon cancer and preliminary data with pancreatic cancer, it is likely that 5-fluorouracil therapy will not benefit patients with MSI pancreatic cancers.

Third, pathways, such as the sonic hedgehog pathway, are being identified which are specifically up-regulated in pancreatic cancer. These pathways provide a wonderful therapeutic window for treating pancreatic cancer.

### **Future Directions**

The next decade will see the emergence of personalized therapy based on the genetic alterations present in a particular patient's cancer. Gastrointestinal oncologists will need a detailed understanding of the emerging genetics of pancreatic cancer.

**Table 1.** Tumor suppressor genes inactivated in pancreatic cancer.

<b>Gene</b>	<b>Chromosome</b>	<b>% of cases</b>
<i>P16/CDKN2A</i>	9p	>95
<i>TP53</i>	17p	50-75
<i>MADH4/DPC4</i>	18q	55
<i>MKK4</i>	17p	4
<i>STK11/LKB1</i>	19q	4-6
<i>TGFβR1, TGFβR2, ALK4, ACVR2, FBXW7, EP300</i>	Various	All <5

**Table 2.** Oncogenes activated in pancreatic cancer.

<b>Gene</b>	<b>Chromosome</b>	<b>% of cases</b>
<i>KRAS2</i>	12p	>90
<i>BRAF</i>	7q	Tumors with wild-type KRAS
<i>MYB</i>	6q	10
<i>AKT2</i>	19q	10-20
<i>EGFR</i>	7p	5
<i>AIB1</i>	20q	60

<b>Table 3.</b> DNA repair genes inactivated in pancreatic cancer.		
<b>Gene</b>	<b>Chromosome</b>	<b>% of cases</b>
<i>MLH1</i>	3p	3-15
<i>BRCA2</i>	13q	7
<i>FANC-C</i>	9q	<5
<i>FANC-G</i>	9p	<5

<b>Table 4.</b> Familial pancreatic cancer.			
<b>Individual/Germ Line Genetic Alteration</b>	<b>Relative Risk of Developing Pancreatic Cancer</b>	<b>Risk of Developing Pancreatic Cancer by 70 Years of Age</b>	<b>Other Cancer Types</b>
<b>No History</b>	1	0.5%	-
<b><i>BRCA2</i> (Breast-Ovarian)</b>	3.5-10	5%	Breast, ovary, prostate
<b><i>P16</i> (FAMMM)</b>	20-34	10-17%	Melanoma
<b>Three or more first-degree relatives with pancreatic cancer</b>	14-32	8-16%	Unknown
<b><i>PRSS1</i> (Pancreatitis)</b>	50-80	25-40%	None
<b><i>STK11/LKB1</i> (Peutz-Jeghers)</b>	132	30-60%	Gastrointestinal, gastroesophageal, small bowel, colorectal, breast

FAMMM = familial atypical multiple mole melanoma syndrome