Review

Pancreatology

Pancreatology 2008;8:110–125
DOI: 10.1159/000123838

Published online: April 1, 2008

Pancreatic Carcinogenesis

Jan-Bart M. Koorstra[a, b] Steven R. Hustinx[a] G. Johan A. Offerhaus[a]
Anirban Maitra[b, c]

[a]Department of Pathology, University Medical Center, Utrecht, The Netherlands; Departments of [b]Pathology, and [c]Oncology, The Sol Goldman Pancreatic Cancer Research Center, Johns Hopkins University School of Medicine, Baltimore, Md., USA

Key Words
Pancreatic cancer · Precursor lesion · Early detection · Mouse models · Genetics

Abstract
Pancreatic cancer is an almost universally lethal disease. Research over the last two decades has shown that pancreatic cancer is fundamentally a genetic disease, caused by inherited germline and acquired somatic mutations in cancer-associated genes. Multiple alterations in genes that are important in pancreatic cancer progression have been identified, including tumor suppressor genes, oncogenes, and genome maintenance genes. Furthermore, the identification of non-invasive precursor lesions of pancreatic adenocarcinoma has led to the formulation of a multi-step progression model of pancreatic cancer and the subsequent identification of early and late genetic alterations culminating in invasive cancer. In addition, an increased understanding of the molecular basis of the disease has facilitated the identification of new drug targets enabling rational drug design. The elucidation of genetic alterations in combination with the development of high-throughput sensitive techniques should lead to the discovery of effective biomarkers for early detection of this malignancy. This review focuses mainly on the current knowledge about the molecular insights of the pathogenesis of pancreatic ductal adenocarcinoma.

Epidemiology

Pancreatic cancer is a disease with a dismal outlook. In the United States approximately 33,000 patients are diagnosed with pancreatic cancer annually, and nearly an equal number will die from the disease, representing the fourth most common cause of cancer-related mortality. Men and women have an approximately equal risk [1]. Worldwide, pancreatic cancer causes an estimated 213,000 deaths each year [2]. For all stages combined, the 1-year survival rate is around 20%, and the overall 5-year survival rate is less than 5%, despite even the most aggressive therapies currently available [1].

A number of risk factors have been identified [3]. Pancreatic cancer is predominantly a disease of the elderly. Pancreatic cancer is rare before the age of 40, and the median age at diagnosis is 73 years. Cigarette smoking is by far the leading preventable cause of pancreatic cancer [4]. Cigarette smoking doubles the risk of pancreatic cancer (relative risk = 2) [3]. Other risk factors include diets high in meats and fat, low serum folate levels, obesity, long-standing diabetes mellitus, and chronic pancreatitis [3, 5–7]. Approximately 10% of patients demonstrate

Jan-Bart M. Koorstra and Steven R. Hustinx contributed equally to this work.

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

Accessible online at:
www.karger.com/pan

Anirban Maitra, MBBS
Johns Hopkins University School of Medicine
1550 Orleans Street, CRB II, Room 341
Baltimore, MD 21231 (USA)
Tel. +1 410 955 3511, Fax +1 410 614 0671, E-Mail amaitra1@jhmi.edu

a familial predisposition for pancreatic cancer, and a subset of these patients harbor germline mutations in *BRCA2, p16/CDKN2A, PRSS1, STK11/LKB1*, or the DNA mismatch repair genes (see further discussion below). In the vast majority of patients with familial risk, however, the underlying genetic predisposition remains unknown.

Complete surgical resection remains the only curative treatment. Studies from high-volume centers with optimal staging report up to a 15–20% 5-year survival rate in patients undergoing surgical resection [8, 9]. The mortality rate is so high because pancreatic cancer usually only produces symptoms when it has already metastasized, and because there are no sensitive and specific tools to detect the disease at an earlier stage. Although multiple histological subtypes of pancreatic cancer have been described, the most common and deadliest form is pancreatic ductal adenocarcinoma [10]. Novel approaches to the management of patients with this aggressive disease are urgently needed.

Research over the last two decades has shown that pancreatic cancer is fundamentally a genetic disease, caused by inherited germline and acquired somatic mutations in cancer-associated genes. A compendium of alterations in tumor suppressor genes, oncogenes, and genome-maintenance genes that are important in pancreatic cancer progression have now been identified (fig. 1). This review focuses mainly on the molecular insights on pancreatic ductal adenocarcinoma and its precursor lesions, including insights gained through experimental models of pancreatic carcinogenesis.

Precursor Lesions of Pancreatic Cancer

Prior to a discussion on molecular genetics of pancreatic cancer, we will briefly discuss the current state of knowledge on precursor lesions of the pancreas. This is essential from the context of separating 'early' genetic changes (i.e. those associated with tumor initiation) from 'late' abnormalities (i.e. those associated with tumor progression). A recent review in *Pancreatology* has extensively discussed the histology and genetics of pancreatic cancer precursors [11]; therefore, we will only discuss these in fleeting detail. Briefly, pancreatic intraepithelial neoplasias (PanINs) are classified into a four tier classification, including PanIN-1A, -1B, -2, -3, reflecting a progressive increase in histologic grade culminating in invasive neoplasia (fig. 2). The lowest grade PanIN lesions can be flat (1A) or papillary (1B), but are characterized by absence of nuclear atypia and retained nuclear polarity. PanIN-2 lesions have micropapillary features with evidence of nuclear atypia and infrequent mitoses, while PanIN-3 lesions (a.k.a. carcinoma in situ) demonstrate widespread loss of polarity, nuclear atypia, and frequent mitoses. In addition to microscopic PanIN lesions, there are now recognized macroscopic (cystic) precursor lesions of pancreatic adenocarcinoma – including intraductal papillary mucinous neoplasms (IPMNs) and mucinous cystic neoplasms. Akin to PanINs, the cystic precursor lesions also demonstrate a multistep histological and genetic progression to invasive neoplasia. Since IPMNs and mucinous cystic neoplasms can be detected by radiologic scans, they represent an opportunity to diagnose invasive pancreatic cancer before it can develop [11].

Tumor Suppressor Genes

Tumor suppressor genes are genes that promote tumor growth when inactivated. Tumor suppressor genes are recessive, i.e. the two copies need to be mutated for loss of function, and they can be inactivated by a variety of mechanisms. First, by an intragenic mutation in one allele (copy of a gene) coupled with loss of the second allele; second, through a deletion of both alleles (homozygous deletion), and third, by hypermethylation of the promoter of the gene-silencing gene expression. In sporadic cancers these alterations are both somatic mutations acquired during life, while patients with inherited forms of cancer inherit one mutant allele in the germline while the second allele is somatically mutated in the cancer cells.

The *p16INK4A/CDKN2A* gene, located on the short arm of chromosome 9 (9p), is one of the most frequently inactivated tumor suppressor genes in pancreatic cancer [12] (table 1). Remarkably, virtually all pancreatic carcinomas have loss of *p16INK4A/CDKN2A* function, in 40% of pancreatic cancer through homozygous deletion, in 40% by an intragenic mutation coupled with loss of the second allele, and in 15% by hypermethylation of the *p16INK4A/CDKN2A* gene promoter [12, 13]. The protein p16 belongs to the cyclin-dependent kinase (CDK) inhibitor family and functions to prevent the phosphorylation of Rb-1 by CDKs, and cyclin D-Cdk4 and cyclin D-Cdk6 complexes, which act as cell-cycle regulators [14, 15]. Loss of *p16INK4A/CDKN2A* results in inappropriate phosphorylation of Rb-1, thereby facilitating progression of the cell cycle through the G1/S transition [16].