Inflammation and Cancer

V. Chronic pancreatitis and pancreatic cancer

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Whitcomb, David C. Inflammation and Cancer. V. Chronic pancreatitis and pancreatic cancer. Am J Physiol Gastrointest Liver Physiol 287: G315–G319, 2004; 10.1152/ajpgi.00115.2004.—Pancreatic inflammation appears to increase the risk of pancreatic cancer. This observation is striking in the hereditary pancreatitis kindreds but also occurs in alcoholic, idiopathic, and tropical chronic pancreatitis and cystic fibrosis. However, the mutations associated with hereditary pancreatitis or cystic fibrosis are not found in sporadic pancreatic adenocarcinomas, suggesting that the effects are indirect by causing recurrent pancreatitis and chronic inflammation. The process of mutation accumulation and clonal expansion that is required for development of invasive pancreatic adenocarcinoma must therefore be accelerated in chronic pancreatitis to account for the high incidence of pancreatic cancer in these patients.

Pancreatic adenocarcinoma remains one of the worst of all cancers. It is difficult to predict, detect, and diagnose and is resistant to all current treatments except early surgery. Other than cigarette smoking (15), pancreatic cancer is associated with few strong and consistent environmental or occupational risk factors. This should not be surprising, because the pancreas is protected from direct contact with the environment and does not play a significant role in detoxification of xenobiotics (as in the liver) nor does it filter and concentrate toxins (as in the urinary system). Recent interest has focused on possible genetic links (22). Indeed, a number of familial syndromes is associated with pancreatic cancer, but only a minority of patients with pancreatic cancer have a strong family history of pancreatic cancer (5, 8). The one consistent risk factor for pancreatic cancer is chronic pancreatitis (25). The origin of chronic pancreatitis and the links between chronic pancreatitis and pancreatic cancer will be discussed.

How does chronic inflammation accelerate the oncogetic process, and why does it take decades before cancer develops in a subset of patients with chronic inflammatory diseases? The first observation is that in many chronic inflammatory diseases, the process driving oncogenesis is likely a “landscaper” defect rather than a germ line genetic “gatekeeper” or “caretaker” defect (12). Landscaper defects, as applied to chronic ulcerative colitis, reflect factors that cause an abnormal microenvironment due to inflammation, and those factors in the microenvironment increase the risk of neoplastic transformation. Indeed, many factors associated with chronic inflammation appear to increase genomic damage and cellular proliferation, which favor malignant transformation of pancreatic cells [see review (7)] including various cytokines, reactive oxygen species, and mediators of the inflammatory pathway (e.g., NF-κB and cyclooxygenase-2), which increase cell cycling, cause loss of tumor suppressor function, and stimulate oncogene expression that may lead to pancreatic malignancy (7). However, inflammation alone usually does not lead to cancer.

ORIGIN OF CHRONIC PANCREATITIS

Chronic pancreatitis (CP) is a progressive, destructive inflammatory process that ends in total destruction of the pancreas and results in malabsorption of dietary nutrients, diabetes mellitus, and severe, unrelenting pain (6). The origin of CP is mixed, with ~70% of the cases being attributed to alcohol abuse even though 95% of alcoholics never develop CP. The remaining cases are classified as idiopathic CP (ICP; 20%), including tropical pancreatitis, which is a major cause of childhood CP in tropical regions, or unusual causes including hereditary pancreatitis, cystic fibrosis (CF), and CP-associated metabolic and congenital factors. However, recent studies (6) reveal that subjects with CP usually have multiple risk factors including a number of underlying genetic susceptibility gene mutations.

The process leading to CP appears to require the interaction of environmental factors, factors that lead to recurrent pancreatic injury [e.g., recurrent acute pancreatitis (RAP)], and/or an altered immune response leading to chronic inflammation and fibrosis (23). Recent genetic studies (24) identified the mechanism leading to RAP in several types of CP. The first discovery, through genetic linkage analysis, was that hereditary pancreatitis is caused by gain-of-function mutations in the cationic trypsinogen (PRSS1) gene. The most common mutation, R122H, alters the target amino acid within the trypsin molecule in the position of trypsin autolysis in conditions with low calcium concentrations such as the pancreatic acinar cell where trypsinogen is synthesized and stored. The second genetic factor linked to CP was the presumed loss-of-function mutations in the pancreatic secretory trypsin inhibitor (SPINK1) gene associated with ICP in children (26) and familial CP (19). The third genetic factor was a variety of CFTR gene mutations identified in ICP and alcoholic CP (4). Functional CFTR is critical for flushing pancreatic enzymes out of the pancreas after they are secreted into the pancreatic duct where the calcium concentrations are high and the trypsin autolysis mechanism is no longer active (23). All of these mutations point to defects in the mechanisms protecting the pancreas from premature trypsinogen activation, which causes injury by activating other digestive enzymes, which, in turn, leads to pancreatic autodigestion and an inflammatory response.
recognized as RAP. The environmental factors associated with CP (e.g., alcohol, tobacco smoking) appear to facilitate RAP by lowering the threshold for initiating trypsinogen activation within the acinar cells, impairing pancreatic duct cell secretion, or modulating the immune system to favor chronic inflammations or fibrosis (6, 23). Genetic alterations in regulators of innate immunity may also play a role in modifying the immune response to RAP to enhance or prolong the inflammatory process or accelerate fibrosis and other complications of CP. The likelihood of having genetic susceptibility to pancreatic injury plus the necessary environmental factors to repeatedly trigger pancreatitis plus an immune response leading to chronic inflammation and fibrosis rather than healing is small and emphasizes the observation that CP is relatively uncommon in humans and is difficult to induce in animals. However, once CP is initiated, it appears to progress relentlessly toward inflammatory destruction of the total organ and provides a milieu for the development of pancreatic cancer.

**CP INCREASES THE RISK FOR PANCREATIC CANCER**

The question of whether or not CP leads to pancreatic cancer arises from the observation that pancreatic cancer itself causes a desmoplasic reaction that resembles CP. Pancreatic cancer can also cause duct obstruction that can also cause distal pancreatic atrophy and fibrosis resembling CP. A clear answer to this question was especially difficult to answer in subjects with alcoholic CP, because the risk of pancreatic cancer appeared to rise appreciably only after several decades of CP (14). The limited number of subjects with severe alcoholic CP who lived for an additional 20–30 yr after development of CP because of the complications of CP or a destructive lifestyle also made it difficult for a single center to address this issue. Lowenfels et al. (14) established an international cooperative study that reported a cumulative risk of pancreatic cancer in subjects with CP of 1.8% after 10 yr and 4.0%, after 20 yr with an standardized incidence ratio of 14.4. This observation has now been supported through multiple epidemiology studies in CP, which all show an increased risk for pancreatic cancer (25). However, the relationship between CP and pancreatic cancer is most clear in studies of patients with childhood onset CP caused by genetic factors such as mutations in PRSS1 and CFTR or in tropical pancreatitis, which is a complex disorder associated with mutations in the SPINK1 gene (20). Because of the early age of disease onset and uncommon use of alcohol, these patients provide significant insight into the relationship between prolonged pancreatic inflammation and development of pancreatic cancer.

Several of the early reports of hereditary pancreatitis kindreds revealed multiple cases of pancreatic cancer (25). The risk became clear after Lowenfels organized another international epidemiology study (13). Eight cases of proven pancreatic cancer were observed against a background expected number of 0.15, giving a relative risk of 53 times normal. The risk of pancreatic cancer markedly increased after the age of 50 yr, which is about 30 yr after the onset of CP. The estimated accumulated risk of pancreatic cancer by the age of 70 in these families is ~40% (13). These studies have been confirmed (10) and extended (15). The EUROAPAC study represents the largest study of hereditary pancreatitis to date and reports the incidence of pancreatic cancer in 112 families from 14 countries ascertained from 418 effected individuals (10). The cumulative risk of pancreatic cancer from symptom onset for the 233 patients with complete information and whose symptoms occurred before cancer was 1.5% [95% confidence interval (CI): 0%, 3.6%] at 20 yr after symptom onset, 2.5% (95% CI: 0%, 5.3%) at 30 yr, 8.5% (95% CI: 1.4%, 15.7%) at 40 yr, 14.6% (95% CI: 13%, 28.0%) at 50 yr, 25.3% (95% CI: 2.5%, 48.1%) at 60 yr, and 44.0% (95% CI: 8.0%, 80.0%) at 70 yr from symptom onset with a standardized incidence ratio of 67% (50%, 82%) (10). There was no difference in risk based on the type of mutations (e.g., PRSS1 R122H, N29I, or no identified mutation). A follow-up report from the original international study by Lowenfels (15) included 497 patients with hereditary pancreatitis, with 19 cases of pancreatic cancer compared with an expected number of 0.33, yielding a risk ratio of 57 (95% CI: 35–90). Together, these studies confirm a high risk of pancreatic cancer in subjects with hereditary pancreatitis, regardless of underlying mutation.

CF is another form of CP with a genetic basis and early onset of disease. CF is an autosomal recessive disorder caused by mutations in the CFTR gene that code for an anion channel that is a critical molecule for proper function of the pancreatic duct cells and other anion-secreting epithelial cells. CFTR conducts both chloride and bicarbonate, and the opening and closing of this channel control the bulk of pancreatic fluid secretion originating in the duct cells. Severe or moderately severe dysfunction of the CFTR-mediated secretory capacity markedly limits the ability of the pancreas to quickly flush digestive enzymes out of the pancreas, especially after trypsin activation, when the risk of autodigestion and pancreatitis is high (23). Severe mutations in the CFTR gene do not lead to pancreatic agenesis, but rather recurrent acute and/or CP. Patients with CF die within the first year of life unless they receive medical intervention. Successful treatment of pancreatic insufficiency, diabetes, pulmonary disease, and nutrition now allow individuals to live well into their thirties and forties. This also means that some of these patients now have long-standing CP, as seen in hereditary pancreatitis. Thus the risk of pancreatic cancer must be considered.

Several groups have evaluated the risk of cancer in adult subjects with CF. In 1993, Sheldon et al. (21) reported a study among 412 subjects with CF and found two cases of pancreatic cancer [0.008 expected, P = 0.001, odds ratio (OR) 61]. The increased incidence of digestive tract cancers, but not cancer in general, was then confirmed by Neglia et al. (18) among 28,511 CF patients in the United States and Canada (risk ratio 6.5) and Europe (risk ratio 6.4). Although only two pancreatic cancers were identified, pancreatic cancers developing during the third decade of life are exceedingly rare, resulting in an OR of 31.5 in this group compared with controls (18).

Tropical pancreatitis (TP) is a form of idiopathic CP seen in tropical Asia and Africa, characterized by abdominal pain, intraductal pancratic calculi, and diabetes mellitus in young, nonalcoholics subjects (17). Augustine and Ramesh (1) reported 22 pancreatic cancers among 266 patients with TP over an 8-yr period (8.3%). In this cohort, the risk was highest after age 40, and patients with TP often had features of dysplasia as well as cancer in resected pancreatic specimens. Chari et al. (3) reported that over a 4.5-yr period, 24 of 185 patients with TP died and that 6 (25%) died of pancreatitis cancer. The average
The association between long-standing CP and cancer has now been clearly established. Pancreatic cancer develops in the setting of CP from all known etiologies but appears to require 30–40 yr of inflammation before an appreciable percentage of CP patients develop pancreatic cancer.

GENES CAUSING PANCREATITIS ARE NOT FOUND IN SPORADIC PANCREATIC CANCERS

If germ-line mutations in the PRSS1 gene and the CFTR gene cause CP and lead to pancreatic adenocarcinoma, are these genes actually oncogenes in which somatic mutations are important in the development of sporadic pancreatic adenocarcinomas? This question has been addressed by Hengstler et al. (9) who analyzed genomic DNA in pancreatic cancer tissue for R122H mutations in the trypsinogen gene from 34 patients and corresponding normal tissue from 28 of these individuals. No mutations were found. Malats et al. (16) investigated the possibility that common CFTR gene mutations were a risk factor for sporadic pancreatic cancers. However, the incidence of deltaF508 mutation and the 5T allele variant was similar to controls. These studies suggest that PRSS1 and CFTR gene mutations are not directly important in the development of pancreatic cancer, but rather lead to a high-risk inflammatory milieu.

PATHWAYS FROM CP TO PANCREATIC CANCER

The pathway between inflammation and cancer involves many steps and converging risk factors. The primary pathway, if there is one, remains an area of research and controversy. However, some aspects of this pathway are becoming clear as new data and perspectives are being organized. The first point is that pancreatic adenocarcinoma is a genetic disorder of pancreatic parenchymal cells and that a general pattern of progressive accumulation of mutations is usually recognized. This pattern has been organized into the Pancreatic Intraepithelial Neoplasm (PanIN) system, which is a standardized system for classification of pathologically abnormal-appearing pancreatic ductal epithelium linked to genetic alterations (11). Multiple studies now confirm that a pattern of mutation accumulation parallels progressive metaplasia and dysplasia, usually beginning with mutations in KRAS2 followed by Id-1/Id-2, p53, cyclin D1 and p16/CDKN2A with DPC4/MADH4 and BRCA2 abnormalities occurring late in the progression of PanIN (25). This pattern of mutations appears to occur in a similar way in sporadic pancreatic adenocarcinoma as well as pancreatic adenocarcinoma arising within the context of inflammation, suggesting that the high risk of pancreatic adenocarcinoma in patients with CP is due to an accelerated process of mutagenesis and mutation accumulation rather than a unique process (25). These appear to be general observations,
however, detailed comparative studies are needed to provide more definitive answers.

**Pancreatic Adenocarcinoma Development as a Complex Disorder**

A complex trait or disorder is a condition that is caused by two or more factors (e.g., gene-gene or gene-environmental interactions) and therefore represents a genetic disorder that does not strictly follow Mendelian inheritance patterns. This is likely the case in pancreatic adenocarcinoma in which affected subjects often have an affected relative, but the inheritance pattern is usually not autosomal dominant or autosomal recessive (2). Hints as to the complexity of pancreatic cancer genetics come from studies on familial pancreatic cancer syndromes that have an increased incidence of pancreatic cancer but also high variability in penetrance and organ specificity among various families with identical genetic defects such as BRCA2 gene mutations. Indeed, there is likely a variety of common genetic mutations that diminish the subjects ability to respond to various challenges and injuries and predispose to progression to cancer.

The importance of environmental risk factors and cofactors cannot be underestimated. The interaction of two environmental factors, the microenvironmental inflammatory milieu created by hereditary pancreatitis combined with the effects of tobacco smoking, illustrates this point. For example, Lowenfels et al. (15) reported an age- and sex-adjusted OR for pancreatic adenocarcinoma in subjects with hereditary pancreatitis (which has an overall OR of 57), which was doubled by tobacco smoking (OR 2.1; 95% CI, 0.7–6.1). Furthermore, the median age of diagnosis of pancreatic cancer was 20 yr earlier in the tobacco smokers. Howes et al. (10) also found a median age of cancer onset in the EUROPAC study of 71 yr in nonsmokers and 56 yr in tobacco smokers. These studies provide striking examples of the compounding effects of risk factors that together contribute to development of a complex disease.

**Breaking the Barriers**

The body uses a series of protective mechanisms and barriers that must be passed before pancreatic adenocarcinoma is established (Fig. 1). For reasons that are not yet clear, only a subpopulation of patients with the hereditary pancreatitis-associated gene mutations progress from recurrent acute pancreatitis to CP (10). These observations suggest variations in the immune response, with some patients recovering, whereas other patients develop chronic inflammation and/or fibrosis, possibly related to genetic variations in the immune regulatory genes. In the context of chronic inflammation, the pancreatic parenchymal cells are exposed to growth and proliferative factors plus agents that can cause DNA damage (7). Smoking likely exaggerates this process. The next barrier is protected by DNA repair mechanisms, which must fail, at least in a subset of cells, for DNA mutations to accumulate. The DNA damage that is not repairable triggers apoptosis, which must fail for mutated clones to survive. As cells become progressively dysplastic, they should be recognized and eliminated by the immune system. This barrier must also fail for pancreatic adenocarcinoma to become established and survive. Clearly, chronic inflammation both drives and accelerates this process, but relevant mechanisms, cofactors, or underlying genetic defects that allow clones of premalignant cells to transverse these barriers are yet to be defined and organized into rational models.

In summary, CP, independent of the underlying cause, over the course of a number of decades, markedly increases the risk for pancreatic adenocarcinoma. The risk is potentiated by known cofactors such as tobacco smoking and, likely, by common genetic factors that are yet to be identified. Studies on genetic and environmental interactions should better define the subset of subjects with CP that are at high risk of malignancy and those at lower risk.

**References**

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