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The Race from Chronic Pancreatitis to Pancreatic Cancer

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The latest data on pancreatic cancer epidemiology were published in 2002 by the American National Cancer Institute. It was confirmed as the 5th leading cause of death from cancer, causing more than 24,000 deaths each year. The fact that nearly all patients die from the disease within one year from the diagnosis was also confirmed, similarly to 15 years ago [1, 2].

A number of studies focused on risk factors; the incidence seems to be higher among men than among women. It also seems higher in the black population rather than in the white population. Furthermore, environmental factors are also associated with the disease: cigarette smoking, meat consumption and low consumption of vegetables. Moreover, the relationship between chronic pancreatitis and genetics in the development of pancreatic cancer was analyzed [3, 4, 5, 6, 7].

Two main studies focused on the association of chronic pancreatitis with pancreatic cancer. The first one, from the International Pancreatitis Study Group, was a large multicenter historical cohort study which assessed the significantly increased risk of pancreatic cancer in subjects with chronic pancreatitis; the association appeared to be independent of sex, nationality and type of pancreatitis [8]. Two years later, Bansal and Sonnenberg confirmed these findings in a retrospective study of data taken from the records of the American Department of Veterans Affairs from 1970 to 1994 regarding diagnoses at discharge [9].

A number of studies also confirmed the association of chronic pancreatitis with pancreatic cancer [10, 11, 12, 13, 14, 15]; moreover, genetic changes in the development of pancreatic cancer were also analyzed [16, 17, 18, 19, 20, 21] even if only a few studies focused on the role of inflammation "*per se*", despite genetic mutations [22, 23].

The way human cancers result from a multistep pathogenesis associated with the progressive accumulation of mutations in proto-oncogenes and tumor-suppressor genes is well-known. This mechanism accounts for the occurrence of dysplastic lesions before cancer development. Types of genetic aberration include mutations in coding or regulatory sequences, changes in ploidy and in genome copy number, amplification, structural rearrangement, homozygous deletion as well as loss of heterozygosity. This mechanism is also thought to be applicable to pancreatic cancer development. K-*ras* mutations are found in a majority of pancreatic carcinomas such as loss of *DPC4/Smad* and *p53* [16, 17, 18, 19, 20, 21].

What appears to be largely unclear at present is the relationship between the early and the late stages of tumor development as well as the role of genetic instability in cancer progression. Indeed, the same genetic alterations can be detected in tissue from both chronic pancreatitis and pancreatic cancer [18, 19]. This common finding uncovered a possible role for cellular environment that

restrains or promotes the emergence of pancreatic cancer is a neoplasia described as a pathological imbalance of tissue-cell interactions. As a matter of fact, changes in the behavior of stromal cells from individuals with cancer and epithelial/stromal interactions have been shown to influence tumor progression [22].

Chronic pancreatitis is characterized by irreversible morphological and functional alterations: inflammation and healing occur simultaneously producing fibrosis.

Cross-talk between mesenchyme and epithelium has been described as a known driver of differentiation and development [24]. The pathogenesis and the progression of chronic pancreatitis are determined from the profile of cytokines persisting in pancreatic tissue: TNF-alpha, IL-6, IL-8, PDGF, TGF-beta. Interestingly, the same pattern of chemokines is found to be increased in pancreatic cancer [23]. Monocytes, which differentiate into macrophages in tissue, represent one of the first recruited effectors of the acute inflammatory response. Once activated, macrophages are claimed to be the main source of growth factors and cytokines, which deeply affect endothelial, epithelial and mesenchymal cells in the local microenvironment [25]. Of note, pancreatic cancer is usually characterized by a remarkable desmoplastic reaction, macrophages being widely represented on histological specimens from pancreatic cancer [4].

A cascade of chemokines is largely secreted from inflammatory cells, representing being one of the ways in which inflammation acts as a tumor promoter [26].

Chronic pancreatitis is characterized by over-production of IL-1, IL-8, EGF, IGF-1, TGF-β1 leading to a stimulatory effect on both angiogenesis and cellular proliferation. Moreover, chronic inflammation of the pancreas is also characterized by production of both IL-6, which shifts myeloid precursors towards a macrophage-like phenotype and TGF-alpha which promotes progressive fibrosis [23]. TNF-alpha is secreted from macrophages and, despite the name, plays an important role in early events in chronic inflammation and cancer. Furthermore, it upregulates both PDGF causing a worsening of pancreatic fibrogenesis and IL-8 enhancing tumorigenic and metastatic effects of human pancreatic cancer cells. One of the biological effects of TNF-alpha is the inhibition of apoptosis of pancreatic cancer cells [24, 25]. This mechanism was described to be mediated through the activation of the transcription factor NF-kappaB, which is constitutively expressed on pancreatic epithelial cells during chronic pancreatitis and cancer. Activation of NF-kappaB may play a central role in the initiation of the relapsing inflammatory process by controlling the transcription of inflammatory genes [27, 28]. The main function of NF-kappaB appears to be transcriptional gene regulation as a transactivating factor; binding of NF-kappaB to specific DNA sequences located in gene promoter regions is a pivotal event in the regulation of transcriptional events by the factor [28]. Furthermore, up-regulation of NF-kappaB also causes an inhibition of apoptosis and stimulation of the inducible form of nitric oxide (iNOS) and cyclooxygenase-2 (COX-2), both well known key mediators of the inflammatory process [29].

Just like NF-kappaB, also COX-2 expression was found to be increased during chronic pancreatitis and pancreatic cancer, in comparison to normal tissue [23, 30, 31, 32]. It is well-known that COX-2 is involved in colorectal cancer converting arachidonic acid to prostaglandins, which, in turn, induce inflammatory reactions in damaged tissues [29]. Moreover COX-2 converts chemical carcinogens to mutagenic derivatives; it allows proliferation and angiogenesis; it inhibits apoptosis in transgenic mice over-expressing COX-2 and it has been shown to display progressive cellular alterations, including dysplasia and loss of normal tissue architecture as well as cellular redifferentiation.

DNA damage found both in chronic pancreatitis and pancreatic cancer is caused from the generation of reactive oxygen (ROS) and nitrogen species produced by leukocytes

and other phagocytic cells in the site of the inflammation. A major target of ROS and free-radical attack is the cellular genome, which is subjected to the formation of numerous genotoxic adducts and DNA strand breaks [33]. Among the most deleterious of ROS-induced adducts is 7,8-dihydro-8-oxoguanine (oxoG). OxoG residues in DNA frequently mispair with adenine during replication, giving rise to transversion mutations. These transversions found in pancreatic cancer are especially prevalent in the mutational spectrum of the tumor suppressor gene *p53* [34].

Repeated tissue damage and regeneration occurring during chronic pancreatitis, in the presence of highly reactive nitrogen and oxygen species released from inflammatory cells, interacts with the DNA of epithelial pancreatic cells resulting in permanent genomic alterations such as point mutations, deletions, or rearrangements.

It is now evident that chronic pancreatitis has a powerful effect on pancreatic cancer development. Chronic pancreatitis could be considered as the field for an attractive environment for tumor growth, facilitating genomic instability and promoting angiogenesis. The inflammatory cells, the chemokines and cytokines regulate the growth, migration and differentiation of all cell types in the tumor microenvironment, including neoplastic cells, fibroblasts and endothelial cells.

The challenge for the future could be to normalize the inflammatory network in order to regain a normal overall host response, thus decreasing the high levels of tumor-promoting properties of the infiltrating cells, such as pro-inflammatory cytokines while increasing their tumor-suppressing properties, such as anti-inflammatory cytokines.

Keywords Chemokines; Genetics; Inflammation Mediators; Pancreatic Neoplasms; Pancreatitis

Abbreviations COX-2: cyclooxygenase-2; iNOS: inducible form of nitric oxide; oxoG: 7,8-dihydro-8-oxoguanine; ROS: reactive oxygen species

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