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EDITORIAL

Inflammation and Pancreatic Ductal Adenocarcinoma: A Potential Scenario for Novel Drug Targets

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Introduction

The relationship between inflammation and the development of cancer has been recognized for a number of years. Well-known examples of this link are: asbestosis/mesothelioma, inflammatory bowel disease/colorectal cancer, chronic viral hepatitis/ hepatocellular carcinoma, *Helicobacter pylori* infection/gastric cancer, Barrett's metaplasia/ esophageal cancer, *Schistosoma haematobium* infection/urinary bladder cancer, human Papillomavirus/ cervical cancer, Hashimoto's thyroiditis/thyroid cancer and human herpesvirus type B/Kaposi's sarcoma [1]. In all these cancers, chronic inflammation produces a cycle of repeated cellular damage and subsequent healing. Cellular injury determines DNA damage with mutations altering proto-oncogene(s) and/or tumor suppressor genes [2]. The healing process consists of cell growing stimulation and growth factor release which would give a helping hand to the proliferation of transformed cells. It is highly likely that similar changes occur within the pancreatic tissue when chronically exposed to inflammatory processes and/or mediators. In fact, while the etiology of pancreatic adenocarcinoma is not yet fully known, epidemiologic evidence from both *in vivo* and *in vitro* studies has demonstrated that inflammation represents an important role in its carcinogenesis [3]. Patients with a rare form of chronic pancreatitis (hereditary pancreatitis, caused by a mutation of the trypsinogen gene on chromosome 7 [4]) have been recognized as being at very high risk for the development of pancreatic adenocarcinoma and have provided sound evidence for a link between pancreatic inflammation and pancreatic adenocarcinoma. The inflammatory process associated with hereditary pancreatitis is progressive, persistent, severe, and affects the whole gland, which may explain the high risk (53 times the risk of unaffected individuals) of subsequent cancer development [5, 6]. An increased risk of pancreatic adenocarcinoma, related to the duration of the disease, is also found in the "classical" non-genetic form of chronic pancreatitis (up to 17 times as compared to age-matched controls [7]). The sequence of persistent inflammation-dysplasia-intraepithelial neoplasia-pancreatic adenocarcinoma has been documented and is related to the loss of tumor suppressor genes and the mutation of proto-oncogenes [8]. The K-*ras* mutation is found in a majority of pancreatic adenocarcinoma, and the additional loss of p53 and DPC4/SMAD functions are strictly related to the carcinogenesis [9, 10]. Multiple inflammatory mediators, including cytokines and other intracellular mediators, are capable of stimulating oncogenic pathways and favor tumor growth and metastasis. Cigarette smoking may induce pancreatic scarring and fibrosis, is associated with higher levels of systemic markers of inflammation and contributes to progression to chronic pancreatitis.

Key words Cyclooxygenase 2; Cytokines; NF-kappa B; Pancreatic Neoplasms; Pancreatitis, Chronic; PPAR gamma; Reactive Oxygen Species

Abbreviations PPAR: peroxisome proliferator-activated receptor

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Novel Drug Targets

Based upon the suggested multiple links between inflammation and pancreatic adenocarcinoma, novel molecular targets in inflammatory pathways are currently being evaluated in experimental and clinical trials aimed at finding new effective weapons against pancreatic adenocarcinoma. These drugs include agents which inhibit or block nuclear factor kappa B (NF-kappa B) activity, reactive oxygen species (ROS), peroxisome proliferator-activated receptor-gamma (PPAR-gamma), cyclooxygenase-2 (COX-2) and cytokines.

Nuclear factor kappa B (NF-kappa B) Activity

NF-kappa B is a transcription factor which regulates the expression of various inflammatory, apoptotic and oncogene genes [11]. NF-kappa B stimulates expression of interleukin-1beta, interleukin-8, tumor-necrosis factor-alpha (TNF-alpha), the inducible form of nitric oxide synthase, and COX-2. Since NF-kappa B regulates both inflammatory and oncogenic pathways, the data showing its upregulation in various malignancies, including pancreatic adenocarcinoma, is of particular interest [1]. Inhibition of NF-kappa B function may be obtained by the administration of drugs with anti-inflammatory properties such as salicylates and corticosteroids, thus resulting in an indirect, non-specific effect. Otherwise, direct inhibition of NF-kappa B activity is related to other more modern strategies including antisense oligonucleotides which block NF-kappa B transcription and other compounds capable of inducing NF-kappa B-related apoptosis [2]. This novel molecular target could act as a strengthener of other treatments in a multi-modal strategy.

Reactive Oxygen Species (ROS)

Some data suggest that oxidative damage represents an important factor linking inflammation and pancreatic carcinogenesis. Smoking has a well-known carcinogenetic role in pancreatic adenocarcinoma [10]; additionally, smoking generates ROS [2], and epidemiological studies indicate that the majority of patients with chronic pancreatitis are heavy smokers. So, the relative contribution of inflammation and exposure to carcinogens present in cigarettes is difficult to separate. Wiseman *et al*. [12] reported that intake of food rich in antioxidants, such as fresh fruits and vegetables, are inversely correlated with cancer of the esophagus, stomach and pancreas. Other authors [13] observed that “traditional” anti-oxidant products, such as beta carotene, selenium and vitamin C, inhibit pancreatic carcinogenesis in rats. One problem inherent to this matter is that the protective effect from oxidative damage seems to be produced by a compound of anti-oxidants rather than by a single agent. Therefore, anti-oxidant treatment (traditional compounds and phytochemicals/free radical scavengers) may have a potential role as adjuvant therapy against neoplasia but, unfortunately, no specific trials are yet available on this subject.

Proliferator-Activated Receptor-Gamma (PPAR-gamma)

PPAR-gamma is a nuclear receptor acting as a transcription factor for the regulation of cellular differentiation, apoptotic pathways and glucose metabolism [14]. Ligands for PPAR-gamma, such as drugs of the thiazolidinedion family (pioglitazone, troglitazone and rosiglitazone [15, 16]) exert anti-inflammatory effects and inhibit cancer cell growth within the pancreas in experimental models [17, 18]. The anti-inflammatory effect is associated with the inhibition of COX-2 and NF-kappa B activity, thus suggesting a complex intracellular pathway [19]. The inhibition of cancer growth is, in part, related to down-regulation of the expression of the vascular endothelial growth factor (VEGF), thus suppressing tumor angiogenesis [18]. Very recently, Fesinmeyer *et al*. [20] have demonstrated that the presence of Pro12Ala variant of PPAR-gamma gene in a cohort of 83 smokers represents an additional risk-factor for developing pancreatic adenocarcinoma. All these data suggest that PPAR-gamma could function as a novel target for the therapeutic control of cancer cell invasion or metastasis [21].

Cyclooxygenase-2 (COX-2)

COX-2, activated by cytokines and growth factors, is involved in the oxidation of arachidonate to form (predominantly) pro-inflammatory prostaglandins and other lipid mediators [22, 23]. The role of COX-2 in pancreatic inflammation is witnessed by its increased expression in pancreatic cells during acute [24] and chronic pancreatitis [25]. Like other tumor types, pancreatic cancer has been shown to overexpress COX-2, which is implicated both in inflammation and carcinogenesis [10]. Recently, Hermanova *et al*. [26] reported a statistically significant difference in COX-2 expression between normal, premalignant and malignant pancreatic tissues as well as a correlation between COX-2 and p53 expression levels in pancreatic adenocarcinoma. Moreover, an accumulation of p53 was associated with COX-2 overexpression in premalignant and malignant ductal lesions. Likewise, other authors [27] have demonstrated a high level of COX-2 expression in intraepithelial-pancreatic-neoplasia (PanIN) lesions. These data suggest that COX-2 could be a therapeutic target at a non-invasive stage of pancreatic carcinogenesis and feasible for chemoprevention patients at high risk of developing pancreatic adenocarcinoma.

Cytokines

Cytokines, released during acute pancreatitis, are capable of inducing cellular damage, and local and distant inflammation with the possible development of multi-organ failure [28]. Similarly, many cytokines (including TNF-alpha, interleukin-1, interleukin-6) and growth-factors (such as transforming growth factors-alpha and beta1, fibroblast growth factor-2 and platelet-derived growth factor) are involved in the pathogenesis of chronic pancreatitis with different mechanisms, including activation of the pancreatic stellate cells [3, 29]. Abnormal cytokine production is reported in many types of cancers resulting in the overexpression of molecules which directly stimulate tumor cell growth (such as growth factors and interleukin-10) or determine suppression of immune-surveillance function [30]. In addition, it has been shown that cytokines with anti-inflammatory properties, such as interleukin-12 and interleukin-15,

are able to inhibit the growth of pancreatic cancer cells *in vitro* [2]. Furthermore, a variety of pro-inflammatory cytokines have been implicated in the anorexia-cachexia syndrome associated with pancreatic adenocarcinoma [31, 32]. Thus, cytokines (TNF-alpha, in particular) represent an important area for a novel therapeutic target to counteract the devastating symptoms associated with late stage pancreatic adenocarcinoma.

Conclusions

Pancreatic adenocarcinoma was responsible for over 8,300 deaths in Italy in 2001 [33] and still remains one of the most deadly of all malignancies throughout the world with a death/incidence ratio of approximately 0.99 [34]. Epidemiological and experimental studies clearly show a reliable link between inflammation and pancreatic adenocarcinoma. Inflammatory mediators can induce genetic damage, inhibition of apoptosis, cell proliferation and tumorigenesis results in the initiation and expansion of cancer cells. Future clinical studies should include the use of targeted anti-inflammatory therapies in prevention and treatment, particularly in those patients who are at high risk of developing pancreatic adenocarcinoma [35]. Considering the relative non-responsiveness of pancreatic adeno-carcinoma to classic antineoplastic agents used alone or in multi-modality combination, both old and new drugs directed at the inflammatory mechanisms may represent a new strategy in an attempt to improve the overall prognosis for patients with pancreatic adenocarcinoma.

Conflict of interest The authors have no potential conflict of interest

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